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)

Tuesday, April 24, 2018

8:00 a.m. to 4:50 p.m.

Day 1

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Jennifer Shepherd, RPh

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ARTHRITIS ADVISORY COMMITTEE MEMBERS (Voting)

Alyce M. Oliver, MD, PhD

Professor of Medicine

Medical College of Georgia at Augusta University

Division of Rheumatology

Augusta, Georgia

J. Steuart Richards, MD

Chief, Division of Rheumatology

Veterans Affairs Pittsburgh Healthcare System

Clinical Associate Professor of Medicine

University of Pittsburgh

Pittsburgh, Pennsylvania

Eric J. Tchetgen Tchetgen, PhD

Luddy Family President's Distinguished Professor

and Professor of Statistics

The Wharton School

University of Pennsylvania

Philadelphia, Pennsylvania

ARTHRITIS ADVISORY COMMITTEE MEMBER (Non-Voting)

James B. Chung, MD, PhD

(Industry Representative)

Executive Medical Director

US Medical Organization

Inflammation Therapeutic Area Head

Thousand Oaks, California

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

MEMBERS (Voting)

Denise M. Boudreau, PhD, RPh

Professor (Affiliate)

Departments of Pharmacy and Epidemiology

University of Washington

Senior Scientific Investigator

Kaiser Permanente Health Research Institute

Kaiser Permanente Washington

Seattle, Washington

Steven B. Meisel, PharmD

Director of Medication Safety Fairview Health Services

Minneapolis, Minnesota

Suzanne Robotti

(Consumer Representative)

Executive Director

DES Action USA

Founder and President

MedShadow Foundation

New York, New York

Christopher H. Schmid, PhD

Professor of Biostatistics Co-Director,

Center for Evidence Synthesis in Health Brown

University School of Public Health

Providence, Rhode Island

Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Professor and Assistant Dean-Designate

Academic Affairs and Assessment

College of Pharmacy

University of Arizona

Tucson, Arizona

TEMPORARY MEMBERS (Voting)

Michael J. Blaha, MD, MPH
Assistant Professor, Cardiology and Epidemiology
Director of Clinical Research
Johns Hopkins Ciccarone Center for the Prevention of Heart Disease
Baltimore, Maryland

Melody J. Cunningham, MD, FAAHPM
Professor of Pediatrics
Director, Pediatric Palliative Care
Fellowship Director, Hospice and Palliative Medicine
University of Tennessee
Le Bonheur Children's Hospital
Memphis, Tennessee

Robert Dubbs
(Patient Representative)
West Palm Beach, Florida

Neil J. Farber, MD
Professor of Clinical Medicine
Medical Director, Internal Medicine Group La Jolla
University of California, San Diego
La Jolla, California

Craig W. Hendrix, MD
Wellcome Professor & Director
Division of Clinical Pharmacology
Johns Hopkins University School of Medicine
Baltimore, Maryland

P. Michael Ho, MD, PhD
Professor of Medicine
University of Colorado School of Medicine
Co-Director, VA Health Services Research and Development Service Denver-Seattle Center for Veteran-centric and Value-driven Research
Denver Veterans Affairs (VA) Medical Center
Denver, Colorado

Julia B. Lewis, MD

Professor of Medicine

Division of Nephrology Vanderbilt Medical Center

Nashville, Tennessee

Richard A. Neill, MD

(Acting Chairperson)

Associate Professor of Clinical Family Medicine and Community Health University of Pennsylvania School of Medicine

Philadelphia, Pennsylvania

E. Magnus Ohman, MD, FRCPI, FESC, FACC, FSCAI
Professor of Medicine
The Kent and Siri Rawson Director
Duke Program for Advanced Coronary Disease
Vice-Chair, Department of Medicine
Development and Innovation
Associate Director, Duke Heart Center
Senior Investigator, Duke Clinical Research
Institute
Duke University Medical Center
Durham, North Carolina

Ruth M. Parker, MD
Professor of Medicine, Pediatrics, and Public
Health
Senior Fellow, Center for Ethics
Emory University
Atlanta, Georgia

Yves D. Rosenberg, MD, MPH

Chief, Atherothrombosis and Coronary Artery Disease Branch Division of Cardiovascular Sciences National Heart, Lung and Blood Institute
National Institutes of Health (NIH)
Bethesda, Maryland

Christianne L. Roumie, MD, MPH

Associate Professor, Internal Medicine and Pediatrics Institute for Medicine and Public Health Vanderbilt University Nashville, Tennessee Staff Physician Veterans Affairs Tennessee Valley Healthcare System
Nashville, Tennessee

Steven F. Solga, MD, AGAF

Associate Professor of Clinical Medicine
Division of Gastroenterology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Sharon Hertz, MD

Director

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Office of Drug Evaluation II (ODE-II)

Office of New Drugs (OND), CDER, FDA

Judith A. Racoosin, MD, MPH

Deputy Director for Safety

DAAAP, ODE-II, OND, CDER, FDA

Valerie Pratt, MD

Deputy Director for Safety

Division of Nonprescription Drug Products (DNDP),

Office of Drug Evaluation IV (ODE IV)

OND, CDER, FDA

Bo Li, PhD

Statistical Reviewer

Division of Biometrics VII

Office of Biostatistics (OB)

Office of Translational Sciences (OTS)

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. NEILL: Good morning, everyone. 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're present, please stand.

My name is Richard Neill and I will be chairing today's meeting. I will now call the joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table. Perhaps we could begin with Dr. Hertz.

DR. HERTZ: Good morning. Sharon Hertz. I'm the director for the Division of Anesthesia, Analgesic, and Addiction Products.

DR. RACOOSIN: Good morning. I'm Judy Racoosin. I'm the deputy director for safety in

the Division of Anesthesia, Analgesic, and Addiction Products, which we'll also refer to today as DAAAP.

DR. PRATT: Good morning. My name is Valerie Pratt. I'm the deputy director for safety in the Division of Non-Prescription Drug Products, which we will refer to as DNDP.

DR. LI: Good morning. My name is Bo Li. I'm a statistical reviewer from the Office of Biostatistics.

DR. HENDRIX: I'm Craig Hendrix in clinical pharmacology at Johns Hopkins.

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

DR. ROUMIE: Christianne Roumie, associate professor, internal medicine, pediatrics at Vanderbilt University and a physician at the Tennessee Valley V.A.

DR. FARBER: I'm Neil Farber, professor of clinical medicine at University of California San

Diego.

DR. PARKER: Ruth Parker, professor of medicine, pediatrics, and public health at Emory.

DR. BOUDREAU: Good morning, Denise Boudreau. I'm a pharmacoepidemiologist and I'm from Kaiser Permanente Washington and University of Washington.

DR. RICHARDS: Good morning. I'm Steuart Richards, a rheumatologist at the VA Pittsburgh Healthcare System.

DR. OLIVER: Good morning. I'm Alyce Oliver at the Medical College of Georgia and I'm an adult rheumatologist.

LCDR SHEPHERD: Morning, I'm Jennifer Shepherd. I'm the designated federal officer for this meeting.

DR. NEILL: Good morning. I'm Richard Neill. I'm a family physician at the University of Pennsylvania, which is in Philadelphia, home of the 2018 Super Bowl champion, Philadelphia Eagles.

DR. TCHETGEN TCHETGEN: Good morning. I'm Eric Tchetgen Tchetgen, statistician, professor at

the University of Pennsylvania.

DR. SCHMID: Chris Schmid, professor of biostatistics, Brown University, unfortunately home of the runner-up to the Super Bowl champions.

MS. ROBOTTI: Hi. I'm Suzanne Robotti. I'm the consumer rep for DSaRM. And I'm the founder of MedShadow Independent Health News and the executive director of DES ACTION USA.

MR. DUBBS: I'm Bob Dubbs. I have no initials after my name anymore. I'm retired. I'm a patient rep.

DR. WARHOLAK: Hi. I'm Terry Warholak and I'm a professor of pharmacy practice at the University of Arizona. And my specialty is quality and safety.

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

DR. LEWIS: Julia Lewis, professor of medicine, adult nephrology, Vanderbilt, and I'm on the Cardio-Renal Advisory Committee.

DR. SOLGA: Steve Solga, University of

Pennsylvania, adult gastroenterology and hepatology.

DR. OHMAN: Good morning. I'm Magnus Ohman and I'm a cardiologist from Duke and Duke Clinical Research Institute. I'm vice-chair of medicine as well. Thank you.

DR. BLAHA: Hi Mike Blaha, director of clinical research at Johns Hopkins Ciccarone Center for the Prevention of Heart Disease.

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

DR. ROSENBERG: Good morning, Yves Rosenberg, division of cardiovascular sciences, National Heart, Lung, and Blood Institute. I'm a clinical trialist.

DR. CHUNG: I'm James Chun. I'm the industry representative. I work at Amgen. I'm the head of inflammation in the U.S. medical organization. I'm a rheumatologist.

DR. NEILL: Thank you. 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 general 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 Statement

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

FDA 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 and Section 712 of the Federal Food, Drug, and Cosmetic Act 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 discussion 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/committeesmeetingmaterials/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 firm 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 any firms at issue. Thank you.

DR. NEILL: Thank you. We will now proceed with the FDA's introductory remarks from Dr. Racoosin.

FDA Introductory Remarks - Judith Racoosin

DR. RACOOSIN: Good morning. I'm Judy Racoosin, the deputy director for safety in the Division of Anesthesia, Analgesic, and Addiction Products. I want to thank you for the time that you've taken today from your busy schedules to assist us with considering the data and questions that will be discussed at this two-day joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee.

This is our third meeting to discuss the issue of cardiovascular risk associated with the use of non-steroidal anti-inflammatory drugs or NSAIDs.

The first meeting, held in 2005, considered data from large clinical outcome trials in a wide

range of indications and epidemiology studies of several individual NSAIDs. And the committee discussed cardiovascular risk with the use of COX-2 selective and non-selective NSAIDs.

Based on the data reviewed and the deliberations of the advisory committee members, FDA concluded that the risk for cardiovascular thrombotic events was present for both COX-2 selective and non-selective NSAIDs.

The data available at the time did not permit rank ordering of the specific drugs regarding cardiovascular risk.

Following the regulatory actions implemented in 2005, celecoxib, marketed as Celebrex, was the only COX-2 selective NSAID still marketed in the U.S.

Pfizer agreed to a post-marketing commitment requested by the agency to conduct a cardiovascular outcomes trial to evaluate the cardiovascular safety of celecoxib. In 2006, Pfizer initiated a trial called prospective randomized evaluation of celecoxib integrated safety versus ibuprofen or

naproxen or, as you'll hear it today, PRECISION.

It was a randomized, double-blind, active-controlled parallel group trial of cardiovascular safety in osteoarthritis or rheumatoid arthritis patients with or at high risk for cardiovascular disease, comparing celecoxib with naproxen and ibuprofen.

While the PRECISION trial was underway, the question of cardiovascular risk with NSAIDs was widely studied in observational databases and meta-analyses of randomized controlled trials.

During 2012 and 2013, FDA reviewed the vast amount of published literature and returned to a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee in 2014 to consider whether this accumulated data changed FDA's understanding of the cardiovascular risk associated with the NSAID class.

FDA presented data related to drug-specific cardiovascular risk, time to event for cardiovascular outcomes, and cardiovascular risk in

vulnerable populations.

Following the meeting, FDA made additional labeling changes to further characterize the cardiovascular risk with NSAIDs, including information on time to event and populations at risk with particular attention to vulnerable populations.

Today, we'll ask you to consider whether the findings of the PRECISION trial support comparable cardiovascular safety for celecoxib as compared with naproxen and ibuprofen, paying specific attention to the doses given.

Because the intent of the PRECISION trial was to assess cardiovascular risk in a population of patients with cardiovascular disease at baseline or at risk for cardiovascular disease, nearly half the patients were taking aspirin at baseline or had it added prior to embarking on the trial.

Therefore, we cannot ignore the potential interactions between aspirin and each of the non-aspirin NSAIDs studied and how these potential drug interactions may have impacted the cardiovascular

outcomes.

There is a long history of in vitro studies characterizing these interactions. We will start the day by reviewing the data on these drug interactions so that you can bear this information in mind when considering the PRECISION trial results.

We will also ask you to discuss the clinical significance of these interactions between aspirin and non-aspirin NSAIDs as well as discussing populations who may be particularly vulnerable to the adverse effects of these drug interactions.

Again, we appreciate your participation in this important meeting and we look forward to a robust discussion.

DR. NEILL: Thank you. We'll now proceed with the FDA's presentation by Dr. Kelty.

FDA Presentation – Jenny Kelty

DR. KELTY: Good morning. My name is Jenny Kelty and I am a medical officer in the Division of Non-Prescription Drug Products. And I will present the regulatory history of the

interaction between aspirin and other over-the-counter non-steroidal anti-inflammatory drugs or NSAIDs.

In my presentation, I will first briefly review the two non-prescription or over-the-counter or OTC regulatory pathways. Then I will discuss the currently available OTC NSAIDs followed by a discussion of the current OTC cardiovascular labeling for NSAIDs.

Finally, I will discuss the history of the OTC labeling of the interaction between aspirin and other NSAIDs.

All OTC drugs are regulated by one of two regulatory pathways, as new drug applications or NDAs, or under the OTC monograph system. This table presents a few of the key differences between the two regulatory pathways.

The primary way that new prescription drugs and Rx-to-OTC switch programs are regulated is through the NDA. For example, ibuprofen and naproxen are NDA products while most aspirin products are marketed under an OTC monograph.

NDAs are product specific and require an application to the FDA for pre-market approval.

On the other side, we have the monograph process, which is a regulatory process that started in 1972 as a way to categorically evaluate the safety and effectiveness of a large number of OTC drugs that were on the market at that time.

A monograph is an FDA regulation that serves as a rulebook for formulating an OTC product by specifying conditions of use under which a drug product is considered generally recognized as safe and effective or GRASE.

The monograph process is a three-step public notice and comment rule-making process. And unlike with NDA products, sponsors of monograph products do not need to submit applications to the FDA as long as they follow the standards set forth in the monograph.

This is a table of currently marketed OTC NSAIDs, their class, and the regulatory pathway in which they are marketed. Although a few OTC aspirin products are approved under a new drug

application, most aspirin drug products are marketed under the tentative final monograph for internal analgesic antipyretic and antirheumatic drug products or TFMIAAA.

The salicylates that are allowed under the monograph are aspirin, buffered aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate. Among these, aspirin and buffered aspirin are the only two cardiovascular-active ingredients in the monograph allowed for use in drugs to prevent ischemic events.

As I mentioned on the previous slide, ibuprofen and naproxen are both marketed under NDAs or abbreviated new drug applications or ANDAs. Most generic drug products are regulated under ANDAs.

Aspirin is available over the counter in several dosage forms, including tablet, buffered tablet, effervescent tablet, chewable tablet, or caplet in immediate-release formulations and as a tablet in enteric-coated formulations in strengths

ranging from 81 to 500 milligrams.

Aspirin is indicated for the temporary relief of minor aches and pains and for the reduction of fever. The tentative final monograph for internal analgesic antipyretic and antirheumatic drug products provides aspirin dosing for these indications for adults and children two years of age and older.

In addition to the OTC conditions of use in the tentative final monograph, FDA regulations at 21 C.F.R. 343.80 include professional labeling for cardiovascular uses of aspirin directed at healthcare professionals.

Professional labeling relevant to OTC drugs is labeling that provides specific information to health professionals for uses not included in consumers' OTC drug labeling.

The professional labeling for aspirin includes uses for vascular indications and revascularization procedures and does not include primary prevention of MI, myocardial infarction, or stroke in healthy patients.

The cardiovascular indications for aspirin are the following; to reduce the combined risk of death and non-fatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, to reduce the risk of vascular mortality in patients with a suspected acute MI, to reduce the combined risk of death and non-fatal MI in patients with a previous MI or unstable angina pectoris, and to reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

The revascularization procedures for which aspirin is indicated are after coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and carotid endarterectomy when there is a pre-existing condition for which aspirin is already indicated.

Now, I will move on to the regulatory history of non-prescription ibuprofen and naproxen. Ibuprofen was first introduced in the United States in 1974 under an NDA as a prescription drug indicated for the treatment of arthritic

conditions.

Subsequently, in 1978, ibuprofen was approved as a prescription drug under an NDA for the treatment of moderate pain. Then, in 1984, ibuprofen was approved for OTC use under an NDA for the temporary relief of minor pain and for temporary fever reduction.

Ibuprofen is available in a variety of strengths and formulations for children and adults and as single-ingredient and combination drug products for adults and children down to six months of age.

Naproxen was first approved under an NDA for prescription use in 1976 and naproxen sodium was approved under an NDA for prescription use in 1980. Subsequently, in 1994, naproxen sodium was approved for OTC marketing under an NDA for the temporary relief of minor aches and pains and for fever reduction.

OTC naproxen sodium is available in adult tablet and capsule dosage forms and as single-ingredient and combination drug products. The OTC

dosing for naproxen sodium is 220 to 440 milligrams every 8 to 12 hours with a maximum recommended adult daily dose of 660 milligrams.

There are currently no pediatric naproxen formulations available over the counter. Currently, both OTC ibuprofen and naproxen sodium are labeled with cardiovascular thromboembolic risk warnings. The cardiovascular thromboembolic risk of NSAIDs was previously discussed at two joint meetings of FDA's Arthritis and Drug Safety and Risk Management Advisory Committees in 2005 and 2014. The details of these meetings will be presented later this morning.

In the next two slides, I will present the OTC NSAID labeling changes that occurred after each of these meetings to inform consumers of the cardiovascular thromboembolic risk of NSAIDs.

Following a 2005 advisory committee meeting, FDA revised the labeling for OTC non-aspirin NSAIDs to include more specific information about the potential cardiovascular risks and information to assist consumers in the safe use of these drugs.

Therefore, OTC ibuprofen and naproxen labels were revised to include the warnings, "Do not use right before or after heart surgery," and, "When using this product, the risk of heart attack or stroke may increase if you use more than directed or for longer than directed."

After the 2014 advisory committees met to discuss data analyses published in 2006 or later, FDA added a new heart attack and stroke warning to the OTC non-aspirin NSAID drug facts label staying, "NSAIDs except aspirin increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or longer than directed."

In addition, the existing, "Ask a doctor before use if you have had high blood pressure, heart disease, liver cirrhosis, kidney disease," was modified to include, "Or had a stroke." And also, common symptoms of heart attack or stroke were added to the label with the statement, "Stop use and ask a doctor if you have symptoms of heart problems or stroke such as chest pain, trouble

breathing, weakness in one part or side of the body, slurring speech, or legs swelling."

In addition to the cardiovascular thromboembolic risks of NSAIDs, studies have demonstrated a pharmacodynamic interaction between aspirin and certain other non-prescription NSAIDs, including ibuprofen and naproxen.

In 2006, based on the available data at that time, FDA published a science paper and healthcare practitioner advisory detailing the pharmacodynamic interaction between low-dose immediate-release aspirin and an OTC dose of ibuprofen.

The science paper stated that existing data using platelet function tests suggested there is a pharmacodynamic interaction between 400 milligrams ibuprofen and low-dose immediate-release aspirin when they're dosed concomitantly.

The data indicated that the timing of dosing of ibuprofen and low-dose aspirin is important for preserving the cardioprotective effect of aspirin. The science paper also stated that the clinical implication of this interaction may be important

because the cardioprotective effect of aspirin when used for secondary prevention of myocardial infarction could be attenuated.

Based on the pharmacodynamic interaction detailed in the science paper, FDA provided recommendations to healthcare providers on how to avoid a potential interaction with concomitant use of ibuprofen and aspirin. FDA recommended that healthcare providers should counsel patients about the appropriate timing of ibuprofen dosing if the patients are also taking aspirin for cardioprotective effects.

FDA recommended that patients taking immediate-release low-dose aspirin and ibuprofen, 400 milligrams, should take the ibuprofen at least 30 minutes after aspirin ingestion or at least 8 hours before aspirin to avoid any potential interaction.

Furthermore, FDA recommended that other non-selective OTC non-aspirin NSAIDs should be viewed as having potential to interfere with the anti-platelet effect of low-dose aspirin until proven

otherwise. And analgesics that do not interfere with the anti-platelet effect of low-dose aspirin should be considered for populations at high risk for cardiovascular events.

Consistent with the FDA recommendations in the science paper, FDA modified the OTC drug facts label of adult single-ingredient and combination ibuprofen products to include this statement, "Ask a doctor or pharmacist before use if you are taking aspirin for heart attack or stroke because ibuprofen may decrease this benefit of aspirin."

Currently, OTC naproxen products do not include labeling regarding the interaction with aspirin. The 2006 FDA science paper referenced a study by Capone, et al. titled Pharmacodynamic Interaction of Naproxen with Low-Dose Aspirin in Healthy Subjects, but stated that there were insufficient data at that time to make a definitive conclusion about the pharmacodynamic interaction between aspirin and naproxen.

Since the 2006 science paper was published, additional data have become available, including

studies published by Oldenhof, et al, Anzellotti, et al, and Gurbel, et al to help elucidate the pharmacodynamic interaction between aspirin and naproxen. The titles of their respective publications are listed on this slide and the details of these studies will be presented later this morning.

Based on the available data, FDA is considering additional or new labeling changes to OTC naproxen products to address this concern and also how the labeling of OTC ibuprofen products may be impacted.

This concludes my presentation of the regulatory history of aspirin and other non-prescription NSAIDs. Thank you for your time.

DR. NEILL: Thank you, Dr. Kelty. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's and industry's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, 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.

We will now proceed with Pfizer's presentations.

Applicant Presentation – Milton Pressler

DR. PRESSLER: Good morning, members of the Advisory Committee, FDA, ladies and gentlemen. I'm Milton Pressler, vice president of clinical development at Pfizer.

In addition to myself, we have another speaker for our session this morning, Dr. Jack Cook, vice president in clinical pharmacology in the global product development section at Pfizer.

The presentation this morning will focus on a request made by FDA regarding the pharmacodynamic effects of celecoxib, ibuprofen, and naproxen as they pertain to the drug effects of aspirin on platelets.

FDA felt it is important for the advisory committee to be aware of data on all NSAIDs that were studied in PRECISION and their potential interaction with aspirin based on the clinical pharmacology data.

So aligned with those requests, Pfizer presents several sets of data today. First, Dr. Cook will provide an overview of the interaction between aspirin and its inhibition of platelet aggregation with the three NSAIDs that were used in PRECISION with an emphasis on Pfizer's medications, namely celecoxib and over-the-counter

ibuprofen.

Specific naproxen data will be deferred to the manufacturer in attendance. Second, Dr. Cook will demonstrate that each of the NSAIDs needs to be considered individually when evaluating how they interact with aspirin, considering both the pharmacodynamics and the pharmacokinetic characteristics of each. Dr. Cook?

Applicant Presentation – Jack Cook

DR. COOK: Thank you, Dr. Pressler.

Good morning. I'm Jack Cook. I'm a vice president of clinical pharmacology at Pfizer. As Dr. Pressler mentioned, I will be presenting data from aspirin interaction studies, examining interactions between NSAIDs used in PRECISION and aspirin with respect to aspirin's effect on platelet aggregation.

My session will focus on celecoxib and ibuprofen. So let's now focus on the mechanism of interaction. The figure on the right depicts the COX-1 enzyme, a homodimer. Aspirin enters a narrow chamber at the active site of the COX-1 enzyme and

then acetylates serine residue shown in green.

This produces a permanent steric hindrance that prevents arachidonic acid from being metabolized at thromboxane A2 at the catalytic site, shown in red. Thromboxane A2 is a potent platelet aggregation agonist; thus lower levels of thromboxane A2 lead to reduced platelet aggregation.

Consider now the administration of an NSAID. Once again, let's look at the figure on the right. Some NSAIDs, like ibuprofen, have the ability to occupy a space near the catalytic site on the COX-1 enzyme. If that site is occupied by an NSAID, an aspirin molecule is sterically hindered from acetylating the serine.

Thus, the NSAID interferes with aspirin's ability to permanently inhibit the enzyme and concomitant administration of NSAIDs may reduce aspirin's ability to inhibit platelet aggregation.

The left-hand side of the slide notes half-life of aspirin, ibuprofen, and celecoxib. Aspirin has a short 15- to 20-minute half-life and thus has

a limited opportunity to acetylate the COX-1 enzyme.

The NSAIDs have half-lives ranging from 2 hours for ibuprofen to 11 hours for celecoxib. Thus, the amount of time that an NSAID can inhibit aspirin's ability to accelerate COX-1 varies with the NSAID.

The right-hand side of the slide considers COX-1 binding. One notes that aspirin's effect is irreversible; thus, anti-platelet effect is sustained for the lifespan of the platelet, which is approximately 10 days.

Ibuprofen reversibly binds the enzyme and has the ability to inhibit aspirin's effect as well as the ability to inhibit arachidonic acid metabolism itself. On the other hand, celecoxib is selective for COX-2 and does not appear to interfere with the COX-1 activity. The celecoxib does not interfere with aspirin's activity at COX-1.

The slide shown now depicts the pharmacodynamics of aggregation that are typically

evaluated in an NSAID-aspirin drug interaction study. In these studies, pharmacodynamic measurements are made after administration of aspirin alone and aspirin in combination with an NSAID.

As you saw in the previous slide, COX-1 produces thromboxane A2, the potent platelet aggregation agonist. This is metabolites to thromboxane B2, a more stable analyte.

Because of the stability, it is thromboxane B2 that is measured. Higher concentrations of thromboxane B2 indicate a higher potential for platelet aggregation. Platelet aggregation is also measured ex vivo by adding various modalities that promote platelet aggregation such as ADP, collagen arachidonic acid. The amount of aggregation can thus be measured directly.

So first, let's consider celecoxib. Since it's a selective COX-2 inhibitor, it's not expected to have significant interactions with a COX-1 enzyme and thus not to alter aspirin's effect on platelet function. This in fact has been confirmed

in a number of studies listed in this table.

One study by Leese demonstrated that celecoxib does not directly alter platelet function. The six other human studies consistently demonstrated the absence of an effect of celecoxib on aspirin's activity on platelet function. Next, I'll present two of these studies.

Leese and colleagues looked at the ability of Naprosyn, naproxen, of a supratherapeutic dose of celecoxib to directly affect platelet aggregation. As you can see from the depiction of the study, the investigators administered the NSAID or placebo for 10 days. Pharmacodynamics are measured as shown on this slide.

The results of this study are presented in this slide. The bar graphs on the left-hand side show the platelet aggregation data for placebo, celecoxib, and naproxen. The gray bar is baseline. The blue bar in each set is the aggregation at 8 hours on day 1 and the yellow bar is aggregation at 8 hours on day 10.

As you can see, the response for celecoxib

and placebo are the same across time, indicating no direct effect on platelet aggregation. The graph on the right depicts thromboxane B2 concentrations. While there were small numeric differences for celecoxib treatment, these differences were not significantly different from baseline.

It is also noted that these differences in thromboxane B2 levels have not translated into interactions with aspirin in the six studies presented in the previous slide. The following slide presents one of those studies.

Li, et al assessed the drug interaction between NSAIDs and aspirin in a two-period trial. In period 1, only aspirin was administered. In period 2, aspirin was administered 2 hours after NSAID administration. Finally, pharmacodynamics were measured in both periods at baseline and after administration.

The results of the Li study are presented in this slide. The left-hand figure depicts aggregation on the Y axis. On the right-hand figure shows thromboxane B2 concentrations. In

each of the colored panels, results for aspirin alone are on the left and aspirin plus NSAID on the right.

Celecoxib is presented in the blue panels. Results are the same for aspirin alone and aspirin with celecoxib and thus indicate no effect of celecoxib on aspirin's ability to inhibit platelet aggregation.

Ibuprofen is presented in the yellow panels. Results are different for aspirin alone and aspirin with ibuprofen and indicate an effect of ibuprofen on aspirin's ability to inhibit platelet aggregation.

So one can conclude that there's an absence of a relevant direct effect of celecoxib on platelet function and there is an absence of impairment by celecoxib on aspirin's effect on platelets.

So now, let's turn to ibuprofen. This slide presents a summary of studies from the literature that have looked at ibuprofen's ability to impair aspirin's effect on platelets. Each of the

checkmarks in the middle column represent a study that found that ibuprofen could attenuate aspirin's inhibitory effects.

Further, many of these studies also looked at the time dependence of that interaction, as noted in the last column. In the next section, I will present further details regarding this aspect.

A study was done by Catella-Lawson that led to a series of studies by Pfizer-Wyeth. The study showed that the administration of a single dose of ibuprofen two hours after aspirin intake preserves the irreversible inhibition of platelet COX-1 induced by aspirin in healthy individuals.

In contrast, inhibition of thromboxane B2 formation and aspirin-induced platelet aggregation was attenuated when a single dose of ibuprofen was given before aspirin. Additionally, administration of 400 milligrams ibuprofen 2, 7, and 12 hours after a daily dose of enteric-coated aspirin was found to inhibit the effect of aspirin on platelets.

Considering these results and the previous

investigations, Pfizer-Wyeth decided to further explore the effect of timing and the sequence of dosing of ibuprofen and aspirin.

A series of three studies were performed to examine the separation of doses of ibuprofen and aspirin in order to find a regimen that would minimize an interaction. The studies examined ibuprofen, 400-milligram administration, and its effect on immediate-release aspirin's ability to inhibit platelet aggregation.

Study AA-02-21 examined how soon one could administrator ibuprofen after aspirin without altering aspirin's effect. Study AA-02-22 examined how soon after ibuprofen one could take an aspirin without altering aspirin's effect. Finally, study AA-04-24 published by Cryer examined an ibuprofen TID regimen in hopes that it would not interfere with the effects of aspirin.

These data were taken into account by the FDA in the drug information for healthcare providers. The OTC label instructs as we have previously heard consumers to talk to their doctor

or pharmacist if they're taking aspirin for heart attack or stroke.

I will show further details about these studies in the following slide. Study AA-02-21 examined the effect of timing when ibuprofen was dosed after aspirin. 31 subjects completed the two-way crossover study and participated in 2 of the 4 regimens where ibuprofen was administered 0, 15, 30, or 120 minutes after aspirin for 6 days.

Pharmacodynamic measurements were taken at baseline on day 1 and 24 hours after the dose on day 6 of aspirin. The results of this study are presented in this slide.

The Y axis depicts the percentage change from baseline of pharmacodynamic response. Thromboxane B2 data are represented as diamonds and platelet aggregation as squares. The X axis presents data for each of the four regimens. The results show an interaction when ibuprofen was administered concomitantly with aspirin on the far left and in fact was still present, though much attenuated at 15 minutes.

At 30 minutes and beyond, greater than 90 percent of the anti-platelet aggregation activity of aspirin was maintained. Thus, this study indicated that patients can initiate ibuprofen treatment 30 minutes after taking immediate-release aspirin.

Study AA-02-22 examined the effect of timing when ibuprofen was dosed before aspirin. 35 subjects completed 2 of the 5 treatment periods where aspirin was administered alone or 2, 4, 6, or 8 hours after ibuprofen for 6 days. Pharmacodynamics were measured at baseline on day 1 and 24 hours after the day 6 aspirin dose.

The results of the study are presented on the graph in this slide. Once again, the Y axis shows the median integer interquartile range for the percentage change from baseline in pharmacodynamic response.

Diamonds depict changes for thromboxane B2 and square depict changes for platelet aggregation. The X axis presents data for the aspirin-only group at the far left and for the four other regimens to

the right. An ibuprofen-aspirin interaction was evident for separation times of 6 hours or less and an interval of 8 hours was needed to achieve 90 percent of the treatment effect of aspirin alone and indicates that a patient should wait at least 8 hours after taking an ibuprofen tablet before taking an immediate-release aspirin.

The results of these two previous studies were considered in the design of study AA-04-24. This study sought to evaluate an ibuprofen-TID dosing regimen that would not interfere with aspirin's effect. This study was published by Cryer in 2005 and examined a regimen where ibuprofen, 400 milligrams, was administered at 1, 7, and 13 hours post-aspirin dosing for 10 consecutive days.

Subjects were pre-treated and continued on a regimen of once-daily immediate-release aspirin. The study duration was 18 days. All subjects were treated with aspirin for those 18 days. They received either ibuprofen or placebo for the final 10 days.

Thromboxane B2 concentrations were measured 24 hours after the previous day's aspirin dose at times shown in the figure. This graph depicts results of the study or this table presents results of the study. Thromboxane B2 inhibition was approximately 98 percent for all times for both placebo and ibuprofen regimens.

This demonstrates a lack of effect of this regimen on the inhibitory effects of aspirin on platelet aggregation. Thus, the study demonstrated a reasonable dose regimen that would not interfere with inhibition of platelet aggregation conferred by aspirin.

In conclusion for ibuprofen, the data demonstrate that ibuprofen can reduce the anti-platelet activity of aspirin. Studies also demonstrated that the degree of ibuprofen's inhibition of aspirin's effect on platelets can be minimized by the timing and sequence of administration of these drugs.

Specifically, the ibuprofen-aspirin interaction can be minimized by taking ibuprofen at

least 8 hours before or 30 minutes after immediate-release aspirin. Thank you. And I will now turn the podium back to Dr. Pressler.

Applicant Presentation – Milton Pressler

DR. PRESSLER: Thank you, Dr. Cook, for your insights on the interaction of these medicines with the pharmacodynamic effects of aspirin on platelet function.

Now, I would like to provide some concluding remarks from a clinical perspective on the laboratory findings that we've just heard.

In summary, multiple studies confirmed no effects of celecoxib on platelet function. There's no evidence of interaction of celecoxib with aspirin in humans. Existing data do demonstrate a pharmacodynamic interaction ex vivo between 400 milligrams of ibuprofen and low-dose aspirin on platelet function. The timing and sequence of ibuprofen dosing can mitigate interaction with aspirin's effects.

However, there are limitations with applying this dosing paradigm to chronic use of prescription

ibuprofen and enteric-coated forms of aspirin.

The clinical relevance of these interactions with clinical biomarkers has not been established. Our presentation with PRECISION later today will provide specific information regarding the relevance of these laboratory observations. Thank you for your attention.

DR. NEILL: Thank you. We will now proceed with Bayer's presentation.

DR. PARADES-DIAZ: Good morning. My name is Alberto Parades-Diaz, director of global medical affairs at Bayer Healthcare Consumer Health. Bayer is the manufacturer of both over-the-counter naproxen sodium under the trade name Aleve and Bayer aspirin.

Aspirin is used for the treatment of minor aches and pain in the over-the-counter setting and for the treatment of acute myocardial infarction and reduction of risk of recurring cardiovascular events under professional care.

Naproxen is a fast-acting and long-lasting analgesic, making it an important option for many

people seeking short-term pain relief. For decades, naproxen sodium-containing products have been and continue to be used safely and effectively for the short-term relief of pain.

There have been more than 1.5 million cumulative worldwide consumer exposures since its over-the-counter launch in 1994. In the over-the-counter setting, it is used at doses up to 660 milligrams daily and labeled for up to 10 days of continuous use.

During this time, no safety signal or trends regarding cardiovascular thrombotic and overall cardiovascular events with or without current aspirin use have been observed with over-the-counter naproxen in post-marketing data.

The investigation of the pharmacodynamic interaction between NSAIDs and aspirin goes back to the study conducted by Catella-Lawson, who demonstrated that ibuprofen interferes with the pharmacodynamic properties of aspirin. Based on these findings, FDA issued a science letter (phonetic) and required a label change in the drug

facts label of over-the-counter ibuprofen-containing products which included the warning, "Ask a doctor or pharmacist before use if you are taking aspirin for heart attack or stroke because ibuprofen may decrease this benefit of aspirin."

Thereafter, Bayer submitted data from two studies, Schiff and Oldenhof, as well as additional published data. The Schiff study demonstrated equal or more than 98 percent mean thromboxane B2 inhibition, similar to that observed with aspirin after seven days of treatment.

The Oldenhof study did not show a pharmacodynamic interaction between naproxen and aspirin after 5 days of concurrent treatment. However, FDA considered that the data were not conclusive and did not rule out a possibility of an interaction.

Subsequent communication with the agency led to the Kontakt study which was assigned to maximize the possibility to observe a pharmacodynamic interaction of immediate-release aspirin and the lowest over-the-counter dose and dosing regimen of

naproxen sodium.

Now, I would like to introduce the lead author of the Kontakt manuscript, Dr. Paul Gurbel, who will provide this overview. Dr. Gurbel?

Industry Presentation – Paul Gurbel

DR. GURBEL: Good morning, everyone. My name is Paul Gurbel. I'm the director of the Inova Center for Thrombosis Research and Drug Development and director of interventional cardiology at the Inova Heart and Vascular Institute. And I hold professor appointments at both Johns Hopkins and Duke University.

This slide shows my disclosures. My laboratory receives private-industry support and the support from the NIH. And also, I receive honorary and consulting fees from these sources.

Now, we're here today talking about platelets. And this slide shows the schematic of platelet activation and a brief touch of the aspirin pharmacology. It's important to note that specific agonists activate platelets through interactions with specific receptors, shown here.

This leads to a cascade of intracellular signaling events, leading to the mobilization of membrane phospholipids, and one of the lipids mobilized is arachidonic acid. Arachidonic acid is converted through cyclooxygenase 1 to a highly unstable intermediate PGH(subscript)2, which then gets converted downstream by thromboxane synthase to thromboxane A2.

This is a very highly labile platelet agonist. This agonist interacts with a specific thromboxane receptor on the surface of the platelet and adjacent platelets, leading to the intracellular signaling events exposing the active IIb/IIIa receptor that is avid (00:56:24/1) for fibrinogen and that's how platelet aggregation occurs.

It's important to note that platelets also secrete granule contents, so these other mediators fuel the amplification process, shown in this slide. And so thromboxane is only one of the many pathways that amplify platelet activation.

It's also important to note that aspirin is

believed to confer its major anti-thrombotic effect through the acetylation of COX-1, as you heard earlier, but there are other important non-COX-1-mediated effects of aspirin that confer anti-thrombotic properties. Thus, an assessment of COX-1 blockade is only a partial surrogate for aspirin efficacy.

There's controversy about what degree of thromboxane inhibition constitutes adequate platelet inhibition. You've seen in the previous speaker various levels of thromboxane inhibition reported.

A question is whether ex vivo thromboxane inhibition above a certain level is really an appropriate surrogate threshold for adequate anti-platelet activity for in vivo thromboxane inhibition. And the gold standard has been suggested to be 95 percent based on a study of 12 healthy volunteers, published many years ago in 1987 by Reilly, et al, demonstrating that in vivo thromboxane biosynthesis, measured by the urinary excretion of the stable metabolite, is maintained

to a substantial degree unless greater than 95 percent inhibition of thromboxane generation ex vivo is achieved.

The one question is whether this threshold really has any translation into clinical relevance. It should be noted that a medical officer with the Division of Cardiovascular and Renal Products opined that no studies with clinical CV outcome endpoints have ever been conducted to confirm the theoretical consequences of being below this threshold.

It should also be noted that other studies and other investigators have not reproduced these findings of Reilly and FitzGerald.

So the key in my mind is what degree of thromboxane inhibition is associated with the inhibition of platelet aggregation, platelet function, since platelet function drives the thrombotic event.

Here, you see a small study, 6 healthy volunteers, showing the relation of serum thromboxane inhibition to inhibition of arachidonic

acid-induced aggregation. And you can see that about 87 percent mean thromboxane inhibition here is associated with a high level of platelet inhibition of function.

So I could suggest that perhaps this 87 percent cut point would be associated with a potent anti-platelet effect and may serve as an appropriate surrogate.

Let's briefly talk about the aspirin and naproxen interaction. You've already seen a little bit about this. Arachidonic acid is converted to PGG(subscript)2 at a tyrosine-385 group. PGG2 is converted to the highly unstable metabolite, PGH2 at the peroxidase active site, and PGH2 is then converted to thromboxane by tissue-specific thromboxane synthase.

The anti-platelet effect of aspirin, as you've heard earlier, is conferred by the irreversible acetylation of the serine 529 group that blocks the access of arachidonic acid to the peroxidase active site, thus the site of potential aspirin and naproxen interaction involving

reversibly binding naproxen and interaction with aspirin and arachidonic acid at the COX-1 molecule.

So what are the studies that have preceded the Kontakt study that I'll mention shortly? The work of Capone of a 4 healthy-volunteer study treated with 100 milligrams immediate-release aspirin for six days followed then by aspirin administered two hours before 500-milligram naproxen BID.

Again, I highlight here 500 because this is higher dose naproxen than OTC naproxen. This was then followed by a washout and then a 500-milligram BID dosing of naproxen two hours before aspirin for six days.

What you see here is that the inhibition of serum thromboxane B2 and also platelet aggregation in urinary 11 dehydro TxB2 levels by aspirin 11-d-TxB(subscript)2 was not significantly altered by the co-administration of naproxen, given either 2 hours after aspirin or in the reverse order.

However, in a small second component to that study of 5 healthy volunteers, there was rapid

recovery of platelet COX-1 activity and function when aspirin was administered synchronously with naproxen, suggesting and supporting the occurrence of a PD interaction between naproxen and aspirin.

A subsequent study by Anzellotti evaluated 6 days of 3 different treatment regimens, separated by a 14-day washout. Here, the sequence is 220-milligram naproxen BID 2 hours before 100-milligram immediate-release aspirin, 100-milligram immediate-release aspirin 2 hours before 220-milligram naproxen BID, and the third, 100-milligram immediate aspirin alone.

What you see here is that the 220-milligram naproxen BID, given 2 hours before aspirin, interferes with the inhibition of serum thromboxane afforded by aspirin and that the interaction was not seen when aspirin was administered before naproxen.

What you also see is the stable thromboxane inhibitory effect of aspirin. Finally, the study of Oldenhof, 5 days of 81-milligram enteric-coated aspirin now, followed by 5 days of aspirin alone, 5

days of enteric-coated aspirin plus naproxen, now 220 milligrams TID, and then 5 days of 81 milligrams enteric-coated aspirin with 1 gram acetaminophen QID.

You see that the anti-platelet effect of EC-ASA once daily was maintained following its co-administration with maximum OTC doses of naproxen or acetaminophen, arguing against any loss whatsoever of thromboxane B2 inhibition.

Thus, with this background are the objectives of the Kontakt study. This study investigated whether concurrent administration of 220 milligram once or twice daily immediate-release naproxen sodium tablets resulted in a pharmacodynamic interaction when combined with a once daily low-dose 81-milligram immediate-release aspirin chewable tablet.

Second objective was to investigate whether the interval between naproxen and aspirin dosing influenced a potential pharmacodynamic interaction. The Kontakt study was a randomized controlled open-label parallel group study.

There was a 6-day aspirin-alone run-in period on days 1 to 6. Again, the aspirin dose was immediate-release, 81 milligram. The naproxen sodium dose administered was 220 milligrams. Following the 6-day aspirin-alone run-in period, there was a 10-day concurrent treatment period on days 7 to 10.

The patients at that time were randomized into 6 groups. The groups shown in orange were administered aspirin and naproxen QD at the same time.

Group 2, the aspirin was administered 30 milligrams after the naproxen QD, serving as a positive control. In group 3, aspirin was administered 8 hours after naproxen QD. Group 4 in green served as our aspirin-alone control group. Group 4 in blue, aspirin was administered 30 minutes before naproxen QD, with the thought being that this could potentially minimize the interaction.

Group 6 was the BID dosing group where aspirin was administered 30 minutes after the first

dose of naproxen and then naproxen was given 12 hours apart.

Importantly, in this study was also an offset phase or a run-out phase of 3 days of aspirin alone during days 17 to 19. This slide shows the methods and analysis. Serum thromboxane was measured at baseline and, on day 7, 16, 17, and 19 of an in-house treatment period serially with the assessment relative to the time of aspirin dosing.

Thromboxane B2 was assessed by a commercially available ELISA kit from Cayman Chemical Company. And as an exploratory analysis, platelet-rich thromboxane was also determined.

The primary pharmacodynamic analysis was the mean and lower bound of the one-sided 95 percent confidence interval for serum thromboxane B2 inhibition at 24 hours post-aspirin administration on day 10 of concurrent treatment. This was felt to reflect a steady state of platelet inhibition induced by aspirin.

This cut point is based on the observation I

showed you on the second slide from Reilly, et al. And finally, the pharmacodynamic interaction was defined to occur when the lower bound of the one-sided 95 percent confidence interval for thromboxane inhibition was less than 95 percent, again based on the cut-off shown from the Reilly paper.

This slide shows the subject disposition. To get enrolled in the study, subjects had to have a serum thromboxane level of greater than or equal to 5,000 picograms per mL. 117 made it into the run-in period. 15 were not randomized for various reasons. 2 of those subjects had arachidonic acid-induced aggregation greater than or equal to 20 percent. 102 were randomized and 80 were evaluable. 22 were excluded with less than 98 percent serum TxB(subscript)2 inhibition 24 hours after the last aspirin dose.

In the run-in period, you see that their mean serum thromboxane level was 95.6, with a range of 78.5 to 97.97 percent.

This is a slide that shows the primary

outcome of Kontakt; again serum thromboxane inhibition at 24 hours post-aspirin administration after 10 days of concurrent treatment. The mean and the lower bound of the one-sided 95 percent confidence interval are presented. The dotted line here is the protocol definition for the interaction.

In our control group in green, the aspirin-alone group, you see very high levels of serum thromboxane inhibition.

In the blue and in the violet group, again, these are the groups that received aspirin 30 minutes before naproxen to potentially minimize an interaction and aspirin 30 minutes after the first dose of naproxen BID. You see that the lower bound of the 95 percent confidence interval barely crosses below the 95 percent definition for resistance.

In the other three groups; the orange group, who received the drug synchronously; the red, the group that would be predicted to have a maximum interaction, and the group that received aspirin 8

hours after naproxen all had much lower preservation of thromboxane inhibition.

If you look at serum thromboxane inhibition at 24 hours post-aspirin administration after 1 day of concurrent treatment, you see no loss of thromboxane inhibition whatsoever.

This slide shows the individual time points during concurrent dosing period in green and during the off-phase in red and the arrows here point to the primary endpoint, which was thromboxane inhibition 24 hours after the 10th day of concurrent dosing.

What you see here in the first 24 hours; there's high levels of thromboxane inhibition. On day 10 of concurrent dosing, there's a loss of thromboxane inhibition that was least in the group that received aspirin before the naproxen with varying levels of loss in the other groups.

Note the aspirin-alone group had stable thromboxane inhibition throughout. By now, we looked at the offset phase. We see a loss of thromboxane inhibition over 24 hours, least in the

group that received the aspirin before naproxen, with recovery of high levels of thromboxane inhibition by day 3, except in the BID dosing group of naproxen.

So in conclusion, after 10 days of concurrent treatment, a pharmacodynamic interaction was observed in all of the concurrent treatment groups. And it persisted for at least 1 day after the end of the naproxen treatment period. After the first day of concurrent treatment, all groups remained above the 95 percent thromboxane inhibition threshold. The degree of the pharmacodynamic interaction was influenced by the timing of aspirin and naproxen dosing and appeared least in the group receiving aspirin 30 minutes before naproxen.

As far as the clinical relevance, the clinical relevance of this pharmacodynamic interaction, particularly with reference to the cut point defining an interaction remains uncertain. There have been no observational studies to link the degree of serum thromboxane inhibition in

cardiovascular outcomes.

No clinical outcomes studies have been specifically designed and conducted to address potential aspirin interactions and, importantly, meta-analysis in the PRECISION study, which we will hear a lot more later on today, do not suggest an increase in cardiovascular risk with concurrent naproxen and aspirin. Thank you for your attention.

Industry Presentation – Alberto Parades-Diaz

DR. PARADES-DIAZ: Thank you, Dr. Gurbel, for your comprehensive review. As you heard from Dr. Gurbel, while uncertainty remains on the relationship between the threshold of thromboxane B2 inhibition and its clinical relevance, Bayer is committed to responsible labeling to guide healthcare providers and consumers, patients on the appropriate use of its products.

As such, Bayer has updated its internal labeling templates for naproxen and aspirin and submitted label change applications around the world. To date, updated labels for aspirin and

naproxen are now effective in most countries.

Most recently, the pharmacovigilance risk assessment committee of the European Medicines Agency reviewed the full body of data on the naproxen-aspirin pharmacodynamic interaction, including data from Kontakt and PRECISION, and concluded that the benefit-risk of naproxen sodium-containing products remains unchanged.

Nonetheless, Bayer has proposed harmonizing the labeling for all oral over-the-counter non-aspirin NSAIDs. This means adding information in the drug facts label under the section, "Ask a doctor or pharmacist before use," that states, "If you are taking aspirin for heart attack or stroke, because naproxen may decrease this benefit of aspirin."

So our presentation ends here. Thanks again for the opportunity to have and review this data. And we're here to respond to your questions. Thank you.

DR. NEILL: Thank you. We'll now take time for clarifying questions for FDA, Pfizer, and

Bayer. If you have a question, please remember to state your name and please direct your attention to Lieutenant Commander Shepherd, who will record an order so that we can make sure that we get to all of you.

State your name for the record before you speak and, if you can, please direct your questions to a specific presenter. Are there any clarifying questions? So I have Dr. Lewis, Dr. Cunningham, and Dr. Farber. Dr. Lewis?

DR. LEWIS: I have two questions for Dr. Gurbel. One, could you help me understand, to keep this in perspective, what the penetration of immediate-release aspirin use is versus enteric-coated aspirin in the market?

DR. GURBEL: I think this question would be better addressed by Bayer.

DR. MALONEY: Hi, Alison Maloney, head of regulatory affairs, Bayer. The penetration of enteric-coated aspirin by volume in the market, based on our data, is 70 percent.

DR. LEWIS: Thank you. I have a second

question for Dr. Gurbel. You alluded to the fact that aspirin's obviously not correlated with CV outcomes, but that it may have other mechanisms other than the thromboxane mechanism for any kind of efficacy. Can you further elaborate on what that might be? And do you know if the thromboxane effect, although separate from whatever these other ones are that you're going to mention to us, does correlate with its effect on those other mechanisms?

DR. GURBEL: So that's a great question. So let's first understand that aspirin acetylates a plethora of proteins in the platelet and in other cells. It has multiple effects beyond solely blocking COX-1. It affects clot porosity. It affects thrombin generation.

So an assessment of aspirin's anti-thrombotic efficacy solely by drilling down just on COX-1 blockade, I think, is tunnel vision, so I think that there are numerous pathways that aspirin affects that mediate an anti-thrombotic property of the drug.

With regards to your second question of what degree of thromboxane inhibition is needed to translate to an increase in clot porosity or effects on thrombin generation, I don't think we have a good handle on that direct relation.

DR. LEWIS: Thank you.

DR. NEILL: Dr. Cunningham?

DR. CUNNINGHAM: Thank you. Melody Cunningham. I have a question for Dr. Gurbel also. So I don't see any data on TID dosing of the 220-milligram doses of the naproxen and it seems like that's often the over-the-counter use, so I wonder if you could speak to that.

DR. GURBEL: So the TID dosing was not one of the 6 arms in the Kontakt study.

DR. NEILL: Dr. Farber?

DR. FARBER: This is also for Dr. Gurbel. I think the studies done before the Kontakt study had obviously very small numbers of patients involved. The Kontakt study itself had a total of 80 patients. And I'm wondering if there was a power analysis to see if there were significant

differences among the groups.

DR. GURBEL: These were not patients. These were healthy subjects. Their age was 37 years.

With regards to the power analysis, I would like to defer that to Bayer.

DR. NEILL: Please state your name.

DR. PARADES-DIAZ: Alberto Parades-Diaz, sorry, Bayer. The design of the study was discussed very closely with the agency, so those numbers on the groups and the treatment groups as well as the dosing were in agreement with the agency.

DR. FARBER: So there was no power analysis done. And is there an analysis in terms of statistical analysis?

DR. PARADES-DIAZ: We have reviewed the data on the whole population that participated in this study, even considering all those who did not achieve 98 percent thromboxane inhibition. There was no difference there.

DR. NEILL: Thank you. I have a question for Dr. Gurbel. Within the Kontakt study, there

were a number of subjects that were excluded by investigator's decision and also 22 excluded because of insufficient thromboxane inhibition. And I wonder if you could just amplify or elaborate a bit on what investigator's decision means and whether or not the 22 excluded might meaningfully represent a similar ratio for those in whom may be taking aspirin or naproxen for their indicated conditions.

DR. GURBEL: I think the reasons for exclusion of the 22 were for reasons that we see in pharmacodynamic studies. There may have been difficulties in getting the blood draws done. There may have been concerns about compliance. There may have been concerns about illicit drug use.

Two patients had arachidonic acid-induced aggregation over 20 percent, so there was a concern about potential non-compliance or aspirin resistance. So we didn't want to enroll any patients who had issues with not complying with the protocol and then also those subjects who may have

had an intrinsic poor response to aspirin.

DR. NEILL: So not being familiar with the general population, do you feel like those numbers would reflect the numbers in a population for whom were using aspirin and naproxen for their indicated uses?

DR. GURBEL: For the subjects who were in this group, they were --

DR. NEILL: No, for the patients that I might have discussions with, whether they should be taking aspirin or naproxen and, if so, together.

DR. GURBEL: Again, the group that were studied were a younger group of volunteers. They were 37 mean age. 30 percent were female. I think it's an older population who uses NSAIDs.

DR. NEILL: Any reason to suspect that that older population has a different manifestation of thromboxane inhibition resistance or whatever you want to call it in this group? No?

DR. GURBEL: Not that I know of.

DR. NEILL: Thank you. Dr. Ohman?

DR. OHMAN: Oops, this is Magnus Ohman. I

have a question for both Dr. Cook and Dr. Gurbel. We've seen different dosings of aspirin, 8,100 milligrams and 325 milligrams for the interaction of these non-steroidal agents.

So the question I have; do we know if this particular dosing of aspirin could have any effect on the interaction? In other words, would it be different if the 325-milligram was used in any of these studies, recognizing that, I believe, Garret FitzGerald showed that the lowest possible dose that causes interaction is about 60 milligrams. And therefore, we're a little bit close to that with the 81.

DR. GURBEL: So I'll go first. We've actually studied this issue of the dose-related effects of aspirin and that was a subject of the ASPECT study, which was a 120-patient double crossover study, looking at 3 doses of aspirin, 81, 162, and 325 daily.

What you see is that COX-1 is inhibited at the lowest dose of aspirin at 81 milligrams. So I do not think it maximally occupies COX-1, maximally

acetylates it at 81. The more intriguing question is whether the COX-1 independent effects of aspirin may be dose-related and we're learning more and more about that regularly.

DR. COOK: Jack Cook, Pfizer, and I have nothing to add.

DR. NEILL: If you could, wait until the microphone gets turned on and if we could get some technical assistance.

DR. COOK: I figured it out. It needed to be on.

DR. NEILL: Thanks. If you could just state your name again, thanks very much.

DR. COOK: Yes, Jack Cook, Pfizer, and I have nothing to add.

DR. OHMAN: I have a follow-on question to Dr. Gurbel's answer.

DR. NEILL: Yes, Dr. Ohman?

DR. OHMAN: You related this to, obviously, arachidonic acid agonist. Have you ever looked at collagen or thrombin to sort of get to the other part of the pathway and what effect that might

have?

DR. GURBEL: That's a great question. Well, what we've seen is that, in the ASPECT study, at low levels of aspirin, 81 milligram, there is complete blockade of COX-1.

So the effect on COX-1 is dose independent. I agree with Dr. Fitzgerald's analysis of 40 milligrams being sufficient. But what we see are dose-dependent effects on collagen-induced aggregation, shear-induced aggregation.

So this is the disconnect between the COX-1 blockade and the non-COX-1-mediated effects of aspirin that I believe are occurring through other pathways in the platelet.

DR. NEILL: Thank you. Mr. Dubbs and then Dr. Weisel?

MR. DUBBS: To follow up on Dr. Neill's question about age, I was concerned that the conclusions and the discussions don't talk about the impacts on different races, the impacts on minorities, males, women, children, and different age categories.

In addition, the drop-out and not following numbers, I wonder about the overall statistical significance. And I have to preface all that by saying that I have no background in any of this, just questions that came to mind.

DR. NEILL: So allow me to ask, is that a question or an observation? If the latter, we can --

MR. DUBBS: It's a question as to why there is no discussion of that. And then you had the additional issue of exclusions. And in much of the discussion, there was no real indication of inclusion, exclusion. So should there be?

DR. NEILL: Would you direct this to Pfizer, Bayer, or FDA?

MR. DUBBS: Everyone.

DR. NEILL: I'll take chair's prerogative. Whoever stands first, I'll recognize you and, if none, I would reassure the panel and industry that, throughout the agenda, staff have taken great pains to assure that we have adequate time to discuss any of the issues, either very specific questions or

more general and important themes that might arise, both later today and tomorrow during the day as well.

Anybody from Pfizer, or Bayer, or FDA?

DR. PARADES-DIAZ: This is Alberto Parades-Diaz from Bayer. We do have the study information, but if you are interested, we could go through the series of recruitment procedures.

DR. NEILL: I just was wondering if non-discussion means non-relevance. In other words, it doesn't matter what the age is; doesn't matter if it was a child; doesn't matter if it was a male, or a female, black, white, et cetera.

Since it wasn't discussed, is it not relevant to the conclusions that you're reaching?

DR. PARADES-DIAZ: Yes. We have very short time limited here, so we cannot put up all this information, but we can provide you with this information.

DR. NEILL: Dr. Cook?

DR. COOK: Jack Cook, Pfizer. The studies we performed are small clinical pharmacology

studies. We do have an upper limit of age that we tend to do in healthy volunteer studies. Studies like this tend to be open to any race and any gender, but the limitation is, because they're small studies, we can't confer anything with any statistical power to doing groups like that.

So the general assumption when you do that is that you have to assume that this is applicable to the larger population. From what we've looked at in the literature, that didn't look like there was anything that suggests that there's an especially vulnerable healthy volunteer population.

DR. NEILL: Thank you. Dr. Meisel?

DR. MEISEL: Steve Meisel with Fairview in Minneapolis, a question for both Dr. Gurbel and Cook. I know that we're here to talk about -- where these studies are represented with over-the-counter doses of naproxen and ibuprofen. But I also know that both of those drugs are used sometimes in prescription doses even though they're over-the-counter forms.

Do you have any data that you could

supplement with prescription doses of these drugs and their interactions that you presented today?

DR. PARADES-DIAZ: I should respond to that question, Alberto Parades-Diaz, Bayer. Dr. Gurbel showed the study from Capone. This is a prescription dose, 500 milligrams BID. There are other studies, also a study from Angiolillo who actually tested naproxen BID, 500 milligrams, in association with esomeprazole versus enteric-coated aspirin and also did not find any interaction after 5 days of intake, concomitant intake.

Yes, those are a couple of studies.

DR. COOK: Jack Cook, Pfizer. In the studies that I presented, other than the Leese study, which uses a supratherapeutic dose for celecoxib to show that there wasn't an interaction there, higher doses were not used, but the good news is, we'll present PRECISION later today and you can see some not biomarker data, but you can see the results of the PRECISION trial, which will encompass higher doses.

DR. NEILL: Thank you. Dr. Lewis?

DR. LEWIS: I just wanted to follow up on our question. And I'm sorry; I can't see your name. I mean, is there any evidence anywhere to suggest that there are racial, gender, or age differences in how these drugs interact with COX, or platelets, or anything? And you sort of touched on it. Is that the answer; there is no evidence? Is there any differences? Since you studied a very somewhat narrow population. Right? That's what you were saying? It's a good question.

DR. COOK: Jack Cook, Pfizer. Not to my knowledge.

DR. LEWIS: Has anyone looked or is there just nothing out there?

DR. COOK: So yes, good question. Jack Cook, Pfizer still. I have not seen a study that looked at gender or race in the interaction.

DR. LEWIS: Thank you.

MR. DUBBS: How about age, children?

DR. COOK: Jack Cook, Pfizer. Again, I've never seen this study with age in the interaction. We don't tend to do many studies in healthy

volunteers in children because of ethical reasons, so no data available.

DR. NEILL: Thank you. Seeing no other clarifying questions from the committee, I'm going to take this opportunity to move us ahead in the agenda two minutes early. We'll now proceed with the FDA's presentations

FDA Presentation – Martin Rose

DR. ROSE: Good morning, everybody. I'm Martin Rose from the Division of Cardiovascular and Renal Products, where I am a clinical team leader, and I'm here to talk about aspirin-NSAID interactions.

So the first topic I'll be addressing today are cyclooxygenase biology. I'm going to be talking about the aspects that are relevant to drug interactions. I'll then move on to the aspirin-celecoxib interaction and then the aspirin-ibuprofen interaction.

So the COXs are a family of enzymes. COX-1 and COX-2 each have two catalytic sites that perform the same two-step reaction. The first site

catalyzes the transformation of arachidonic acid to prostaglandin, G2 or PGG2.

PGG2 is a short-lived compound that is quickly catalyzed to PGH2 by the second catalytic site. COX-1 is the dominant COX in platelets, which will be the major focus of our concern today.

PGH2, the end product of the COX catalytic pathway, is a very short-lived product that is quickly transformed to clinically important eicosanoid endpoints by isomerases that are variably expressed in human tissues.

Platelets contain thromboxane synthase, which transforms PGH2 to thromboxane A2. As you've heard, thromboxane A2 is a platelet activator and is also a vasoconstrictor.

The cardioprotective effects of aspirin are related to aspirin-induced inhibition of platelet activation. Activation of platelets leads to release of platelet contents and platelet aggregation.

Platelet activation is triggered by tissue collagen, thrombin, and adenosine diphosphate or

ADP, and other natural and synthetic compounds. The released ADP and thromboxane A2 are capable of activating other platelets, leading to a chain reaction of platelet activation.

Activated platelets stick to fibrinogen and Von Willebrand factor, promoting the formation of platelet plugs and clots.

Aspirin irreversibly acetylates COX-1, which then deactivates the enzyme. Aspirin has a 20-minute half-life in blood, but its duration of biological activity is a function of the turnover of the irreversibly acetylated COX enzymes.

In most cells, COX activity is largely normalized in a few hours after exposure to aspirin through replacement of the acetylated enzyme and by newly formed enzyme. However, platelets have no nuclei and thus cannot make new COX. The duration of COX inhibition in platelets is a function of platelet turnover. Mean platelet survival is about 10 days, so platelet turnover is slow enough that once-daily dosing of aspirin is adequate to create continuous inhibition of thromboxane synthesis.

Also, platelets are affected by lower doses of aspirin than other tissues. The IC50 of aspirin for COX-2 is about 10 times the IC50 for COX-1, making aspirin probably the most COX-1 selective of the OTC NSAIDs. Unlike aspirin, NSAIDs are competitive inhibitors of the COX enzymes, so their effects are dependent on concentration.

The many NSAIDs have different specificity for COX-1 and COX-2. So this slide depicts the specificity of individual NSAIDs, calculated as the log of IC50 for COX-2, divided by the IC50 for COX-1. Those NSAIDs that are near to the left margin of the plot are more selective for COX-2, while those on the right are more selective for COX-1.

We'll be focusing today on four of these products, denoted by the red arrows. From left to right, they are celecoxib, ibuprofen, naproxen, and aspirin. Note that this graphic, like most others of its type, is a compilation of data from other sources, meaning that there were varying methods that were used to assess the specificity of the individual NSAIDs.

Thus, the magnitude of differences in specificity between any two products on this graph may not be accurately shown.

So the sponsor has shown you a classic cartoon of COX-1 inhibition by aspirin or ibuprofen and the mechanism of action of the two drugs. We now know that timing is critical for this interaction.

If an NSAID already occupies the COX-1 binding site, aspirin cannot access the serine acetylation site. If that occurs, then later when the serum concentration of the NSAID falls and the NSAID no longer inhibits COX-1, the patient will have unprotected platelets that could be activated and trigger a thrombotic event.

In aspirin-NSAID interaction studies, timing of binding site occupancy by an NSAID could be affected by several factors that are under the control of the experimental team, including the timing of the last NSAID dose prior to aspirin administration, the timing of the next NSAID dose following aspirin, the aspirin formulation,

immediate release versus enteric coated, the dose of the NSAID, and possibly the dose of aspirin.

So here is some information on the pharmacologic properties of the drugs we'll be talking about. These data ought to inform how these drugs are dosed in interaction studies.

Dosing shown for the NSAIDs includes OTC recommendations as well as the highest prescription dose recommended for arthritis. I won't go through all the data on this chart, but I will note that aspirin has professional labeling that recommends a daily dose of 75 to 325 milligrams for several indications relating to coronary artery conditions.

Immediate-release aspirin has a very short Tmax, about 30 minutes if it is chewed and about an hour if it is swallowed whole. The half-life is 20 minutes, as others have said.

Enteric-coated aspirin has a much later Tmax that varies from about 3 1/2 to 6 hours, so it's much slower than immediate-release aspirin. The other NSAIDs described here have longer half-lives than aspirin. However, the half-life of ibuprofen

is only about 2 hours compared to 11 hours or more for celecoxib and naproxen.

Here are some U.S. sales data. I think they come from a different source than our friends from Bayer used. These are from IMS and they refer to 81-milligram tablets. One caveat with respect to these data is that IMS tracks only about 50 percent of aspirin sold in the U.S., so the numbers I'm about to tell you may be off.

Over the last few years, enteric-coated aspirin has constituted about 58 percent of 81-milligram aspirin sales and immediate release about 42 percent, so that's pretty consistent with the data that Bayer quoted of about 70 percent for enteric-coated aspirin.

So how do we assess aspirin's effects on platelet aggregation? Dr. Gurbel has talked a little bit about thromboxane B2 generation. That particular test has been used in many of the interaction studies.

When platelets are activated, they release thromboxane A2, which is rapidly hydrolyzed to

thromboxane B2, which is a more stable molecule that can be measured reproducibly in serum. The test is quite simple. 1 mL of whole blood in a glass tube is maintained at 37 centigrade for 1 hour, allowing the blood to clot.

The serum is spun off and the concentration of thromboxane B2 is assessed, now often with an ELISA kit. TxB2 inhibition is calculated as 1 minus the concentration after an intervention, divided by the concentration before an intervention, times 100.

FDA believes that cardioprotection requires thromboxane inhibition of 95 percent or more based on a paper by Reilly and FitzGerald that's been alluded to.

Being conservative, we think that the lower limit of the 95 percent confidence interval for inhibition should be no less than 95 percent. So let's move on to the aspirin-celecoxib interaction studies. The first study I'm going to talk about is a study that was performed by G.D. Searle, now a part of Pfizer.

This was called the Wilner study in Pfizer's submission. They didn't talk about the data, but I think it's useful to talk about them. This was a single-center, phase 1, randomized, double-blind, parallel trial, placebo controlled in confined healthy volunteers.

On days 1 to 4, patients received celecoxib, 200 milligrams, twice daily or matching placebo. On day 5, all subjects received a single dose of their randomized study drug and one tablet of immediate-release aspirin at a dose of 325 milligrams and that occurred at 8:00 a.m.

The pharmacodynamic assessments were assessment of thromboxane B2 in whole blood and various platelet aggregation studies.

I'll focus on the thromboxane data. You can see them circled up there. The slide shows the thromboxane B2 mean concentration on day 5, at hour 0, when aspirin was given, and then hours 2 and 8.

Note that inhibition is low at hour 0, but rapidly reaches levels greater than 99 percent,

which are maintained in both arms from hour 2 to hour 8. Thus, this study does not distinguish celecoxib from placebo in terms of its interaction with the anti-platelet effects of aspirin. There's absolutely nothing here.

The other study cited by the sponsor confirmed this finding and also show that celecoxib alone has no clinically important effect on platelet function. Significantly, some of those studies used aspirin at a dose of 100 milligrams. Here, it was 325.

So we can conclude and we agree with the sponsor that studies on volunteers demonstrate that celecoxib, 200 milligrams, BID does not interfere with the anti-platelet activity of aspirin at doses recommended for cardioprotection in the United States, which are 75 to 325 milligrams.

Let's move on to the aspirin-ibuprofen interaction. The sponsor has shown you the results of the Catella-Lawson publication and we agree with their interpretation of that paper. They've also shown you information about Wyeth Study 02-21d, but

our interpretation of the results is not quite the same as theirs.

This was a two-period crossover trial in volunteers. It was intended to investigate the effects of variations in the timing of administration of IR, immediate-release chewable aspirin and ibuprofen, 400 milligrams.

Aspirin was given before ibuprofen for 6 days, with doses separated by 0, 15, 30, or 120 minutes. Thromboxane B2 formation and arachidonic acid-stimulated platelet aggregation were assessed before the first dose and 24 hours after the last dose of aspirin.

Here are the results for thromboxane inhibition on day 6. You can see that the curve rises up from the left margin from around 70 percent at hour 0, around 90 percent at 15 minutes, about 95 percent at 30 minutes, and then up to nearly 100 percent at an hour.

The 30-minute data have a lower limit of the 95 percent confidence interval that goes below 95 percent. The confidence interval at 2 hours, the

lower limit, is well above 95 percent. We would consider the half-hour results as borderline. That is half-hour separation between the two doses; may not be enough.

Two hours is clearly long enough to wait. One hour may be enough. But regardless of that, these results cannot be extrapolated to an aspirin formulation that has slower absorption, i.e., enteric-coated aspirin.

We also don't agree with the sponsor's interpretation of Study 02-22. This is a Wyeth study to assess the effects on aspirin pharmacodynamics in subjects who received aspirin after dosing with ibuprofen, with varying separation of the doses.

Thirty-nine subjects were enrolled in a two-period crossover study and received two of the following regimens for 6 days: ibuprofen, 400 milligrams in the morning in each case, and then IR aspirin, 81 milligrams given 2, 4, 6, or 8 hours later. And again, they looked at thromboxane inhibition and platelet aggregation 24 hours after

the last aspirin dose.

So here's the results. You can see that, excuse me, the dark line is thromboxane inhibition. And again, I'll focus on that. You can see that it rises up from 50 percent at hour 2 to about 70 percent at hour 4, a little less than 90 percent at hour 6, and 90 percent at hour 8. All mean values were less than 95 percent, the lower limit of the confidence interval, which is what FDA looks at, was less than 95 percent in every case.

So we don't agree with how Pfizer interprets this study. We do agree with the sponsor regarding the results of the Cryer study, which was 02-24.

That's the last data slide I'll show you. So with respect to the aspirin-ibuprofen interaction, we reached the following conclusions. The available data indicate that ibuprofen administration can attenuate the anti-platelet effects of aspirin.

The timing of dosing of ibuprofen relative to aspirin and the aspirin formulation have major effects on the extent of the interaction. And a

3 or 4 times daily ibuprofen regimen that does not attenuate the anti-platelet effect of enteric-coated aspirin has not yet been identified. Thank you.

FDA Presentation – Sudharshan Hariharan

DR. HARIHARAN: Good morning, everyone. I am Sudharshan Hariharan, a team leader in Division I of the Office of Clinical Pharmacology at FDA. I'll be presenting FDA's perspective about the pharmacodynamic drug interaction between aspirin and naproxen.

So here is an outline for my presentation. I'll start with background, then provide a brief overview of some of the earlier studies that evaluated the interaction between aspirin and naproxen.

Then I'll talk about how those studies shaped our understanding of this drug interaction that led to collaborative efforts between Bayer and the FDA in designing a drug interaction study between low-dose aspirin and OTC doses of naproxen.

I'll then talk about the results and the

conclusion of the study, ending with an overall summary of our thoughts on this topic.

As you have heard from the presentations this morning, FDA released a science paper in 2006 which warned healthcare practitioners of the potential for ibuprofen to interact with aspirin's anti-platelet effect.

The mechanism of interaction between aspirin and non-selective NSAIDs competing for COX-1 has been described in detail in the earlier presentations today. The interaction liability for ibuprofen naturally raised questions for naproxen, another non-selective NSAID which is approved for prescription use and as an over-the-counter medication.

The only publications available by 2006 on naproxen-aspirin interaction were not conclusive; however did not rule out the potential for an interaction.

Since then, there has been significant interest for understanding the interaction between these two drugs. The important pharmacokinetic

features of the drugs of interest have also been presented earlier. However, to quickly recap the information pertinent to this interaction is the half-life of aspirin, which is short about 15 to 20 minutes, and acts by irreversibly acetylating the COX-1, whereas naproxen has a much prolonged half-life of about 12 to 17 hours and acts by reversibly binding to COX-1.

Also important to note is the time to reach peak plasma concentration for aspirin, which is relatively short for immediate-release formulation compared to enteric-coated aspirin.

As mentioned before, naproxen is a non-selective NSAID. Shown on this slide is a comparison of COX-1 activity, measured as inhibition of serum thromboxane B2 between low-dose aspirin, and OTC, and prescription doses of naproxen.

As seen from this table, the inhibition of serum thromboxane B2 at 24 hours post-dose on day 5 following treatment with immediate-release aspirin, 100 milligrams, for 5 days is about 99 percent.

The inhibition of serum thromboxane B2 following naproxen prescription doses at 440 milligrams BID is as high as 99 percent, but only at earlier time points closer to Tmax. At later time points, inhibition of COX-1 activity gradually wanes off with declining plasma exposures to naproxen.

The inhibition of COX-1 activity is attenuated even further with the OTC dose of naproxen at 220 milligrams BID compared to the higher prescription dose of naproxen.

So overall, in concept, this data raises a potential for an interaction between aspirin and naproxen. If following co-administration, naproxen blocks the binding of aspirin to COX-1. Then the anti-platelet effect mediated by COX-1 may attenuate over time as naproxen's exposure starts to decline, while aspirin is long cleared from the body because of its short half-life.

One of the earlier evidences for an interaction came from a study from Capone and colleagues, who characterized the interaction

between aspirin and naproxen in washed platelets in vitro.

The plots on the left-hand side show the inhibition of platelet thromboxane B2 as a function of concentration of aspirin in the top panel and naproxen in the bottom panel. The open circles correspond to the test condition and the presence of .5 micromolar arachidonic acid, the substrate. And the closed circles correspond to arachidonic acid at a concentration of 10 micromolar.

As you can see from the plot in the top panel, the inhibition of platelet thromboxane B2 by aspirin was not influenced by the concentration of arachidonic acid, suggesting the irreversible binding of aspirin to COX-1.

On the other hand, naproxen showed a severalfold shift in IC50 values with increase in concentration of arachidonic acid, confirming the reversible nature of binding to COX-1.

Further, the author studied whether pre-incubation of naproxen had the ability to affect the irreversible inhibition of aspirin to COX-1.

Shown on the right-hand side is inhibition of thromboxane B2 for aspirin at two different concentrations in the presence of varying concentration of naproxen.

As seen from the plot, naproxen reduced aspirin's inhibition of thromboxane B2 in a concentration-dependent fashion and, interestingly, this effect started to occur at concentrations lower than those inhibiting platelet COX-1 activity.

When naproxen was shown to interfere with aspirin's COX-1 activity in vitro, the interaction was not very evident in some of the clinical studies conducted earlier.

Capone and colleagues evaluated the drug interaction potential between naproxen, 500 milligrams given twice daily, where the first dose was taken 2 hours before or after low-dose immediate-release aspirin. The other publication, Oldenhof and colleagues, studied the interaction between naproxen, 220 milligrams TID, concomitantly administered with low-dose enteric-coated aspirin.

I'm not showing the results of these studies as it was presented by Bayer already. These studies did not show a clear signal for an interaction, however likely because the doses of naproxen were high.

As we know, naproxen at higher exposures, due to its inherent activity on COX-1, may compensate for any modest interaction seen during co-treatment with aspirin.

Another limitation of these studies was that there was no evaluation or limited evaluation during naproxen washout. Samples were collected only up to 36 hours post-dose in the Oldenhof publication and the results may also be confounded because of a presence of a few outliers.

Nevertheless, an interaction with aspirin could exist in the naproxen washout phase, although for a shorter duration as plasma exposures of naproxen start falling below the levels required for optimal COX-1 activity.

While there were studies conducted with prescription and higher OTC doses of naproxen, it

was important to understand the liability of interaction at lower OTC doses of naproxen with low-dose aspirin.

That question was answered to an extent by the study conducted by Anzellotti and colleagues, where subjects were administered naproxen, 220 milligrams, BID either prior to or after 100 milligrams immediate-release aspirin, separated by 2 hours for 5 days.

Following a 14-day washout, subjects were administered aspirin alone for 5 days. As seen in this plot on the right-hand side, the inhibition of serum thromboxane B2 was attenuated when naproxen was administered 2 hours prior to aspirin.

The interaction was minimized when aspirin was administered 2 hours prior to naproxen, which highlighted the importance of the timing of administration of these agents to one another.

The interaction becomes more prominent at later time points, as seen by the 48-hour post-dose, as exposure to naproxen wanes over time. While the Anzellotti study provided good insight at

the potential for interaction with naproxen, there were still some unanswered questions which formed the basis for the design of the study negotiated between Bayer and the FDA.

The interaction liability following the lowest naproxen OTC dose of 220 milligrams once daily was still unknown. Hence, that was important to characterize it in the study.

Also, if there was an interaction, it was important to explore different timing of administration of these drugs to mitigate or minimize an interaction. With higher naproxen doses, it became important to follow patients longer after the last dose of naproxen, with an expectation to identify an interaction during naproxen washout.

Additionally, we wanted to increase the sensitivity of the study to identify an interaction if one truly exists. So this was done by increasing aspirin compliance and establishing a higher threshold of serum thromboxane B2 inhibition with aspirin treatment.

So after many iterations, the final design of this interaction study was agreed upon between Bayer and the FDA. This was a randomized, controlled, open-label, parallel group study to determine the effects on anti-platelet activity when OTC naproxen, 220 milligrams, was added to low-dose aspirin.

The study consisted of three periods, run-in, treatment, and wash-out. And all subjects had to be off any NSAID therapy for the last 7 days to be considered for enrollment.

During the run-in period, subjects were administered immediate-release aspirin for 6 days. Subjects were administered the first dose at the clinical study site on day 1. They were instructed to take the doses on days 2 and 3 in an outpatient setting.

To ensure compliance, subjects were instructed to return to the clinical study site on days 4 to 6 for site staff to observe dosing at the target dosing time. On day 7, the first day of treatment period, only subjects who met the

following criteria were randomized. That is patients who took aspirin for 5 out of 6 days, including day 6, had baseline serum thromboxane B2 on day 1 greater than 5,000 picograms per mL and those who had day 7 platelet aggregation less than 20 percent.

Subjects with serum thromboxane B2 inhibition was less than 98 percent on day 7 were randomized but considered non-evaluable for analysis. A high baseline serum thromboxane B2 and greater than 98 percent inhibition criteria was set to ensure compliance with aspirin and increase the sensitivity to identify an interaction in this study.

The eligible subjects were then randomized to 6 different treatment groups, the details of which will be presented on the next slide. The treatment period lasted for 10 days and, on day 17, subjects entered the washout phase, where treatment with naproxen was discontinued, but were treated with immediate-release aspirin for 3 days, until day 20.

The following are the treatment arms in the study. I'll start with highlighting group 4, where subjects received immediate-release aspirin, 81 milligrams once daily for 10 days. This group serves as the control for this study.

Subjects in group 1 received aspirin with naproxen, 220 milligrams, once daily, given concomitantly, representing the reality that these drugs are frequently taken together. Group 2 subjects received naproxen, 220 milligrams, once daily 30 minutes before aspirin. This functions as the positive control for the trial to ensure assay sensitivity if an interaction does indeed exist.

In group 3, naproxen was administered 8 hours prior to aspirin. And this arm was designed to identify how many hours after a naproxen dose that aspirin can be taken without loss of platelet inhibition.

Group 5 was the best-case scenario, where aspirin was administered 30 minutes prior to naproxen. And in group 6, subjects received naproxen, 220 milligrams, as a twice-daily regimen,

but the first dose was administered 30 minutes before the aspirin dose.

This arm would represent a more frequent administration of an OTC dose with an interest in study findings during naproxen washout. The primary pharmacodynamic variable in this study was serum thromboxane B2 and I'll be showing the results only for this primary variable.

Blood samples for pharmacodynamic assessments were collected on days 7, 16, 17, and 19, which represent the first day of treatment with naproxen, the last day of treatment, day 1 of naproxen washout, and day 3 of washout, respectively.

The primary pharmacodynamic endpoint was the mean and the lower bound of the corresponding one-sided 95 percent CI for serum thromboxane B2 at hour 24 on the last day of treatment.

A positive interaction was defined as the one-sided 95 percent CI for serum thromboxane B2 at hour 24 on day 16 to be less than 95 percent. This slide shows the results for the primary endpoint.

Y axis is percent serum thromboxane B2 inhibition. The dotted horizontal line represents the 95 percent inhibition threshold.

As you can see from this plot, all the groups showed an interaction by the defined criteria in the study, except group 4, which was the control arm. The interaction was the greatest in group, where naproxen was administered 30 minutes prior to aspirin and the interaction was among the lowest when aspirin was administered 30 minutes prior to naproxen in group 5.

Interestingly, aspirin, when dosed 8 hours after a naproxen once-daily dose, did not prevent an interaction. It is also interesting that naproxen, when dosed twice daily and 30 minutes prior to aspirin dose, showed a minimal interaction; however with the caveat that these inferences are made based on the primary endpoint.

The results for the primary endpoint convey only a part of the story. It is important that we go through the time course of serum thromboxane B2 as collected in the trial during both the treatment

and washout period for a more in-depth understanding of this drug interaction.

For the next few slides, you will see the time course for serum thromboxane B2 inhibition for various treatment groups. The time course will be shown in 4 panels, where each panel, starting from left to right, indicate the first day of treatment, the last day of treatment, day 1 of naproxen washout, and day 3 of washout.

As seen before, Y axis is serum thromboxane B2 inhibition and the dotted horizontal line represents 95 percent serum thromboxane B2 inhibition. As seen from the panels below, the control group consistently showed serum thromboxane B2 inhibition greater than 95 percent all throughout the study, assuring treatment compliance with aspirin.

This slide shows the time course for concomitant administration of naproxen and aspirin. As seen from panel 1, there is no interaction at any time points on the first day of treatment, likely because the platelet inhibition with aspirin

following 6 days of treatment prior to the first dose of naproxen overwhelms any modest interaction.

However, as naproxen starts to interfere with aspirin's anti-platelet activity, the platelet inhibition effects at the end of the dosing interval begin to attenuate, as seen with the last day of treatment.

This is representative of a scenario where there is a modest interaction not picked up at earlier time points because of the inherent platelet inhibition effects of naproxen. However, it shows up at later time points as naproxen's exposure begins to wane off while aspirin is long eliminated from the body.

It is important to note that, although this interaction is picked up at the last day, this could have taken its effect any time during the concurrent treatment period between days 8 to 16. The interaction is also evident during the first day of naproxen washout.

However, as naproxen continues to be eliminated, serum thromboxane B2 recovered to near

maximal inhibition by day 3, with repeat daily administration of once daily low-dose aspirin.

A similar trend across these panels is seen in the rest of the groups, except group 6. Here, shown in this slide is the time course for group 2, where naproxen was administered 30 minutes prior to aspirin. Consistent with the primary endpoint results, a greater magnitude of interaction is evident in this group.

However, by day 3 of wash-out, inhibition of serum thromboxane B2 recovered to near maximal values. Again, following a similar trend across these panels, the interaction is minimized when naproxen is administered 8 hours prior to an aspirin dose.

Shown on the slide is the results for group 5, where aspirin was administered 30 minutes prior to naproxen. Though there was minimal interaction during the treatment period, the lower bound of the 95 percent CI for serum thromboxane B2 dropped closer to the 90 percent threshold during the first day of washout, suggesting that a modest

interaction for a few hours during the first day of washout may exist even when aspirin is administered 30 minutes prior to naproxen.

This slide shows the time course of serum thromboxane B2 inhibition from group 6. The time course for this group is slightly different in a way, that there is only a modest interaction seen during the treatment period with a lower bound of the 95 percent CI dropping just below the 95 percent threshold.

However, a larger interaction is seen during naproxen washout, which is not completely recovered even after 3 days of naproxen discontinuation. This suggests that, when naproxen is dosed more frequently or when higher doses of naproxen is used, an interaction still exists but is just delayed until treatment with naproxen is discontinued and the concentrations start falling through a range where there is just enough naproxen to block aspirin's anti-platelet effect, but not high enough to compensate for loss of aspirin's effect.

This was a key finding from the study and raises an important point about the studies conducted earlier with higher naproxen dose, that if subjects were followed post-treatment discontinuation long enough, an interaction was likely evident.

So to summarize, the study conclusions were that an interaction between aspirin and naproxen is evident from the study and the results are highly internally consistent with regard to the relative timing of administration of aspirin and naproxen.

The interaction is greater when naproxen is dosed 30 minutes prior to aspirin. Interaction is also evident even when naproxen is dosed 8 hours prior to aspirin; however, only at later time points or at trough.

Interaction between low-dose aspirin and the lowest naproxen OTC dose may be minimized when aspirin is taken 30 minutes prior to naproxen. However, these results are only applicable to immediate-release aspirin formulation and not to enteric-coated aspirin.

An interaction with the twice-daily OTC naproxen regimen exists. However, the interaction is delayed and happens following discontinuation of naproxen, than during treatment with naproxen.

Our overall summary is that this study establishes unequivocal evidence for a drug interaction between aspirin and naproxen. As Bayer concluded, the clinical relevance of this interaction on CV outcomes remains unknown because the quantitative relationship between serum thromboxane B2 inhibition and risk for CV outcomes is not available.

However, it is not unreasonable to assume that the relationship between serum thromboxane B2 inhibition and risk for CV outcomes is a continuum that any decrease from the optimal level of inhibition that can be achieved with aspirin could be considered a clinically relevant interaction.

The relative timing of administration of these drugs may minimize interaction. And finally, higher prescription doses of naproxen are a more frequent regimen of naproxen OTC doses may provide

maximal suppression of serum thromboxane B2 during concomitant treatment with aspirin.

However, an interaction would likely exist following discontinuation of naproxen. That concludes my presentation. Thank you.

DR. NEILL: Thank you. We will now take a slightly more than 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.

Panel members, at your place, you will find a boxed lunch pre-order form. If you'd like lunch, please complete it. Return it to the kiosk that's outside the meeting room along with $11. Your boxed lunch at noon is going to be waiting for you in the reserved panel lunch room, 1504, at the lunch break.

We'll meet back here at 10:35. Thank you.

(Whereupon, at 10:17 a.m., a recess was taken.)

DR. NEILL: We'll now continue with another FDA presentation from Dr. Racoosin.

FDA Presentation – Judith Racoosin

DR. RACOOSIN: Good morning, again. This morning, I'm going to be reviewing with you the regulatory history regarding the safety issue of thrombotic cardiovascular events associated with NSAID use.

I'll briefly review some drug utilization data on the three NSAIDs that we're going to be discussing today, celecoxib, ibuprofen, and naproxen. Then I will review the regulatory actions that followed advisory committee discussions on the safety issue in 2005 and 2014.

This figure shows prescription utilization of celecoxib, ibuprofen, and naproxen single-ingredient products from outpatient retail pharmacies. Among the 3 NSAIDs examined, ibuprofen single-ingredient products accounted for the majority of prescriptions dispensed over the period.

Over these last 12 years, the number of prescriptions for ibuprofen and naproxen single-ingredient products, have increased while the

number of prescriptions of celecoxib have decreased.

This figure shows patient utilization of celecoxib, ibuprofen, and naproxen single-ingredient products from outpatient retail pharmacies, stratified by patient age group. The largest amount of use for ibuprofen single-ingredient products was among patients age 25 to 44.

For celecoxib and naproxen single-ingredient products, the largest amount of use was among patients aged 45 to 64. This figure shows OTC sales data from retail stores. During the five-year period displayed, sales of ibuprofen and naproxen single-ingredient products sold in the over-the-counter setting remain relatively steady, with 173 million packages of ibuprofen and 64 million packages of naproxen sold in 2016.

Now, I'll move on to describe the circumstances that led to the discussion of NSAID-associated cardiovascular thrombotic risk in 2005 and the subsequent regulatory actions taken by FDA.

Over the early part of the 2000s, data began to emerge from large, randomized, controlled clinical trials demonstrating cardiovascular thrombotic risk with the COX-2 selective NSAIDs, a subgroup of the broader class of NSAIDs.

In September of 2004, the voluntary withdrawal of rofecoxib by Merck Pharmaceuticals following identification of an elevated risk for cardiovascular events in a clinical trial of familial adenomatous polyposis created an opportunity for an FDA review of the available clinical trial data in epidemiologic studies for all the COX-2 selective and non-selective NSAIDs.

On February 16th to 18th, 2005, a joint meeting of FDA's Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee was convened to consider this data.

The trials reviewed at the meeting included efficacy trials in rheumatologic conditions, outcome studies with pre-specified gastrointestinal and cardiovascular safety endpoints, and other trials and conditions where inflammation was

postulated to have an etiologic effect, including familial polyposis and Alzheimer's disease.

Data was presented for trials involving rofecoxib, celecoxib, and valdecoxib, and other COX-2 selective NSAIDs. However, I will focus on the trials that included celecoxib, given the focus of today's meeting.

The anti-platelet trialist collaboration composite endpoint is composed of cardiovascular and unknown cause deaths, non-fatal MI, and non-fatal stroke, both ischemic and hemorrhagic. The APTC composite endpoint was used in many of the trials, but not all of them.

This table summarizes the key results of 4 large trials conducted for celecoxib in various disease indications. Over the next few slides, I will display the analyses of cardiovascular composite safety endpoints in these various studies.

My intent in showing the figures over the next few slides is to show the varying results across doses and indications in which celecoxib was

studied. Please note that, for the most part, these cardiovascular outcome analyses were conducted post hoc.

The Celecoxib Long-term Arthritis Safety Study or CLASS in which celecoxib was compared to diclofenac or ibuprofen was designed primarily as a gastrointestinal safety study. This slide shows a post hoc analysis among patients not taking aspirin in the CLASS trial. The figure on the left shows a similar time-to-event plot for the composite cardiovascular event endpoint for celecoxib compared to the combined group of diclofenac- and ibuprofen-treated patients.

The figure on the right breaks out the 3 treatment groups. Note that the Y axis has expanded somewhat to show the differences between the three groups. Celecoxib is the line denoted with the circles.

The adenoma prevention with celecoxib or APC trial and the prevention of spontaneous adenomatous polyps or PreSAP trial were both conducted to determine whether celecoxib prevented the

development of colorectal adenomas.

The APC study showed a dose response for the cardiovascular endpoint with celecoxib 400 milligrams BID having the highest rate of events and celecoxib 200 milligrams BID having an intermediate incidence compared to placebo. In contrast, the PreSAP study showed little difference between the celecoxib 400-milligram once-daily arm and the placebo arm.

In the Alzheimer's Disease Anti-inflammatory Prevention Trial or ADAPT, celecoxib was compared to naproxen or placebo on the composite cardiovascular outcome of cardiovascular death, MI, stroke, congestive heart failure, and transient ischemic attack. There was little difference between the placebo and the celecoxib 200-milligram BID arm. However, the rate of the composite endpoint for naproxen was significantly worse than placebo.

Although FDA concluded that the COX-2 selective NSAIDs celecoxib, rofecoxib, and valdecoxib all were associated with an increased

risk of serious adverse cardiovascular events compared to placebo, FDA did not determine that the COX-2 selective agents conferred a greater risk than the non-selective NSAIDs.

FDA's overall conclusion was that the available data were best interpreted as being consistent with a class effect of an increased risk of serious adverse cardiovascular events for COX-2 selective and non-selective NSAIDs.

The short-term use of NSAIDs to relieve acute pain, particularly at low doses, was not considered to confer increased risk of serious adverse cardiovascular events with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass graft surgery.

Finally, the benefit of valdecoxib was not considered to outweigh its risks because of its additional side effect of life-threatening skin reactions such as Stevens-Johnson Syndrome.

Based on these conclusions, FDA recommended that valdecoxib be withdrawn from the market and

that the labeling of all NSAIDs be modified to include a boxed warning, highlighting the potential for increased risk of cardiovascular events with these drugs as well as describing the well-known, serious, and potentially life-threatening gastrointestinal bleeding associated with their use.

The labeling revision also included the addition of a contraindication for use in patients immediately post-op from coronary artery bypass graft surgery. And there was a requirement for a medication guide to be dispensed with every prescription NSAID to better inform patients about the cardiovascular and gastrointestinal risks.

As you heard earlier, the non-prescription NSAID labeling was also revised to reflect this information.

Finally, the agency requested that the sponsors of the non-selective NSAIDs submit a comprehensive review and analysis of available controlled clinical trial data to further evaluate the potential for increased cardiovascular risk.

The information submitted from the development programs of the non-selective NSAIDs did not provide additional actionable data. The agency recognized that we needed comparative data on the cardiovascular thrombotic risk of COX-2 selective and non-selective NSAIDs.

That led to the request for Pfizer to conduct a comparative trial of celecoxib to naproxen and ibuprofen for cardiovascular safety outcomes. You're going to hear a lot more about the PRECISION trial today, so I will defer discussion of the trial to subsequent speakers.

I'll mention that the European Medicines Agency or EMA was also conducting a review of this issue in the same time frame as FDA. The most distinctive difference from FDA's conclusions was that EMA considered the COX-2 inhibitors to have a more severe cardiovascular risk than the non-selective NSAIDs and thus required a contraindication for the COX-2 inhibitors, saying that they must not be used in patients with established ischemic heart disease and/or

cerebrovascular disease, or in patients with peripheral arterial disease.

Now I'll move on to describe the circumstances that led to a follow-up discussion of NSAID-associated cardiovascular thrombotic risk in 2014 and the subsequent regulatory actions taken by FDA.

While the PRECISION trial was underway, a tremendous amount of energy and effort in the academic and regulatory community was focused on studying the question of cardiovascular safety with the NSAID class.

These efforts included conduct of meta-analyses of randomized controlled trials as well as the examination of this risk in numerous observational databases. By 2014, when FDA held a follow-up advisory committee to discuss the accrued data, there were more than 75 observational studies published on the topic, not to mention numerous commentaries, scientific assessments of biological plausibility, and review papers.

We distilled the most commonly examined

questions to the ones listed on this slide. Are there data to better refine the understanding of time to event for cardiovascular risk with NSAIDs? Is it an early hazard versus an increased risk with cumulative use, or perhaps both depending on the population?

Are there data to support differential cardiovascular risk across specific NSAIDs? And are there data that suggest specific vulnerable populations for NSAID-associated cardiovascular risk?

In February 2014, the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee convened to consider these questions. Based on FDA's review and the advisory committee's recommendations, the prescription NSAID labels were further revised regarding cardiovascular risk.

With regard to time to event, we added that the risk of MI or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID. With regard

to dose response, we added that the risk appears greater at higher doses.

With regard to product-specific risk, we concluded that the accrued evidence suggested that cardiovascular risk is not the same for all NSAIDs. However, there is not adequate information to determine whether the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

With regard to the at-risk population, we added that NSAIDs can increase the risk of MI or stroke in patients with or without cardiovascular disease or risk factors for cardiovascular disease.

A large number of studies support this finding with varying estimates of how much the risk is increased, depending on the drugs, doses, and populations studied. With regard to vulnerable populations, we added that, in general, patients with cardiovascular disease or risk factors for it have a greater likelihood of MI or stroke following NSAID use than patients without these risk factors, because they have a higher risk at baseline.

Specifically, patients treated with NSAIDs following a first MI were more likely to die in the first year after the MI compared to patients who are not treated with NSAIDs in the first year after their first MI.

Finally, we added data showing that there is an increased risk of heart failure with NSAID use. A safety labeling change was required for the NSAID class in July 2015 to incorporate these labeling revisions as well as implement an updated NSAID class labeling template.

The revised labeling was approved for all NSAID class members in May of 2016. Over the last several years, EMA has also continued to review the data on cardiovascular risk with the NSAID class. They have concluded that the effects of diclofenac and high-dose ibuprofen on the heart and circulation when given systemically are similar to those of selective COX-2 inhibitors.

That brings us to today's discussion. We'll hear Pfizer's presentation of the PRECISION trial and then, after lunch, FDA will present our review

of the trial.

DR. NEILL: Thank you. We'll now continue with Pfizer's presentations.

Applicant Presentation – Milton Pressler

DR. PRESSLER: Good morning, again. Ill reintroduce myself. I'm Milton Pressler, a vice president of clinical development at Pfizer. In addition to myself, we have two other speakers in our session this morning; Dr. Steven Nissen, professor and chair of cardiovascular medicine at the Cleveland Clinic.

Dr. Nissen is a recognized expert in coronary disease and the principal investigator of the PRECISION study. Dr. Stanley Cohen, clinical professor of rheumatology at the University of Texas Southwestern, is a well-known expert in the treatment of rheumatologic diseases and a clinical investigator for the PRECISION trial.

We have additional experts available to answer your questions; from Cleveland Clinical Research, Katherine Wolski, the clinical trial statistician; from Pfizer, Dr. Richard Xia, Wayne

Wisemandle, Amanda Jones, Vera Frajzyngier, and David Kellstein, experts in the various subjects listed.

Now, before we get to the results of PRECISION, I will provide a brief background on the events leading up to FDA's request for the trial and its deliberations during the conduct of the study.

The presentation this morning will provide the rationale for undertaking a CV outcome study for symptomatic treatments of chronic osteoarthritis and rheumatoid arthritis. We will contextualize the circumstances leading up to PRECISION, so the key design elements are understood.

We will present the PRECISION study results followed by a rheumatologist's perspective and review the results from PRECISION, what has been learned, the impact on the understanding of cardiovascular safety of the drugs tested.

Finally, I will return to the podium to provide the sponsor's view of the clinical and

regulatory implications of PRECISION for prescribers.

There's a major need for treatments of chronic pain in osteoarthritis and rheumatoid arthritis in this country. A recent survey showed 52.5 million adults or 22.7 percent of the adult population had doctor-diagnosed arthritis in the United States.

Arthritic conditions are amongst the most common causes of disability. And the numbers are increasing as the population ages. Roughly 100 million prescriptions are written for NSAIDs per year. Pain is the main complaint of osteoarthritis patients and the focus of treatment. NSAIDs are commonly used, especially for osteoarthritis, and an attractive alternative to opiates or acetaminophen in these patients.

Millions of adults are regular users of NSAIDs even though they may cause GI bleeding and renal impairment. No single NSAID is universally effective, so it's important to have choices, especially considering that different patients have

different risk profiles.

Now, I'm going to spend a few slides complimenting and supplementing what Dr. Racoosin just shared with us, providing again a little rendition on the history of cardiovascular risk with COX-2 inhibitors.

Celecoxib was approved in December 1988. Rofecoxib was approved in May 1999. There was widespread adoption due to longstanding GI concerns with non-selective NSAIDs. Let's focus first on rofecoxib.

The VIGOR trial in the year 2000 was a turning point in our collective understanding of cardiovascular safety of these drugs. Increased cardiovascular risk was found with rofecoxib at 50 milligrams versus naproxen at 1,000 milligrams, dosed in rheumatoid arthritis patients.

The increased cardiovascular risk was then confirmed with a lower dose of rofecoxib, 25 milligrams, in the approved study. So rofecoxib was withdrawn by the manufacturer.

This slide shows Kaplan-Meier curves of

adjudicated serious cardiovascular thrombotic events from the VIGOR study. Some 8,000 patients were randomized into the study and, as you will note, those patients who are on a 50-milligram daily dose of rofecoxib had a greater incidence of serious cardiovascular thrombotic events as compared to naproxen at a dose of 500 milligrams twice daily.

The hazard ratio of rofecoxib versus naproxen was 2.4. A second key study for rofecoxib was APPROVe(superscript)2. The APPROVE trial was a double-blind, placebo-controlled trial of rofecoxib with 2,586 patients having colonic polyps. Cardiovascular safety was assessed by the incidence of APTC events and, as Dr. Racoosin has defined, APTC stands for Anti-Platelet Trialists Collaboration and refers to the composite of cardiovascular death, non-fatal MI, and non-fatal stroke.

Rofecoxib significantly increased the risk of APTC events at the approved arthritis dose of 25 milligrams per day.

Now, let's turn to, again, the history on another COX-2 inhibitor, celecoxib. Celecoxib has been evaluated in long-term trials of patients with colonic polyposis and Alzheimer's disease. APC and PreSAP were trials in patients with colonic polyps. Doses and regimens were different from those typically used in patients with arthritis.

Roughly 2,000 patients were randomized in APC whereas around 1,500 were randomized in PreSAP. Preliminary studies had suggested that higher doses of celecoxib might be required to treat polyps than to treat arthritis pain.

ADAPT was an NIH trial in patients 70 years and above with a family history of Alzheimer's disease. Celecoxib at a dose of 200 milligrams twice daily was compared to a lower dose of naproxen, 220 milligrams twice daily, and to placebo. Around 2,500 patients were randomized.

This slide depicts the results from all three celecoxib trials as whisker plots. In APC, top sets of rows, there was a greater risk of cardiovascular events at both doses of celecoxib

that were tested. Hazard ratios of 2.8 and 3.4 were observed and these were statistically significantly different than placebo.

In contrast, PreSAP found a lower hazard ratio of 1.2 on 400 milligrams once daily of celecoxib. And similarly, ADAPT reported a hazard ratio of 1.14 at 200 milligrams twice daily of celecoxib.

Neither of these hazard ratios were statistically significantly different than placebo. Please note that, in ADAPT, naproxen at a lower dose of 220 milligrams twice daily showed a hazard ratio of 1.57 versus placebo.

The Coxib and Traditional NSAID Trialists Collaboration, better known as the CNT group, performed an individual patient-level meta-analysis of randomized controlled trials which collected findings from 280 trials of NSAIDs versus placebo and 474 trials of one NSAID versus another.

However, most of these were short-term studies of arthritis patients that contributed few, if any, cardiovascular events. The bulk of the

cardiovascular events arose in a small number of trials such as those we've just reviewed in studies of colonic polyps, Alzheimer's disease, and rheumatoid arthritis.

Shown here are CNT's published results for celecoxib by dose. The data in the box outlines the approved doses for use of celecoxib for arthritis in adults in the United States. The effects of celecoxib were significantly dependent upon dose. Please note the 200-milligram daily dose representing around 75 percent of prescriptions at a rate ratio of 0.95 versus placebo, whereas the 400-milligram daily dose had a rate ratio of 1.29. The 800-milligram daily dose shows a rate ratio of almost 3.

This slide shows some key comparisons from the CNT meta-analysis regarding the rate ratio of APTC events for the drugs studied in PRECISION.

It's important to note that the CNT analysis reported both the results of direct as well as indirect comparisons. Let me explain what we mean by that.

The first, second, and third rows were estimates derived from trials that actually directly compared the outcomes of drugs tested. In contrast, the fourth and fifth rows highlighted in the green box show the findings that were imputed from indirect comparisons.

Celecoxib had a similar rate ratio to naproxen and ibuprofen when these two drugs were compared in clinical trials, these first two rows. PRECISION now expands on the comparative risks of celecoxib, ibuprofen, and naproxen in a large-scale cardiovascular outcomes trial where cardiovascular events are pre-defined and adjudicated.

The implications of the foregoing trials and meta-analyses of trials were examined in the 2014 advisory committee meeting and the deliberations that followed within the FDA as Dr. Racoosin has reminded us. This slide provides some key takeaways from the 2014 and 2015 deliberations.

The initial impression that naproxen carried lower cardiovascular risk was related to the effect that its estimated effect was driven by indirect

comparisons that were largely dominated by comparison with high doses of the COX-2 inhibitor with the most consistent CV toxicity, rofecoxib, 50 milligrams a day.

In general, the observational studies were consistent with greater cardiovascular events with rofecoxib than with celecoxib, but reported similar cardiovascular risks for celecoxib versus non-selective NSAIDs.

The advisory committee understood that PRECISION would provide a randomized controlled comparison and test these hypotheses in a head-to-head comparison of naproxen versus other NSAIDs and celecoxib. I'd now like to introduce Dr. Nissen, who will present the results of the trial.

Dr. Nissen?

Applicant Presentation – Steven Nissen

DR. NISSEN: There we go. Thank you. Ladies and gentlemen, it's a great pleasure to present to you the results of the PRECISION trial, which stands for Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or

Naproxen. My disclosures are shown here. I do work on clinical trials with industry. However, for many years, actually, two decades, I have asked companies to direct any honoraria, speaking, or consulting fees directly to charity so that I receive neither income nor a tax deduction in order to be completely independent.

Before I begin, I really wanted to thank Drs. Hertz, Racoosin, and the review division for the consistent advice we've received from them during the conduct of this very long and very challenging clinical trial. I also wanted to thank Bob Temple, who couldn't be here today, who was also very helpful to us.

This presentation reflects the views and analyses of the academic leadership of the PRECISION trial. My travel expenses are funded by the academic coordinating center, the Cleveland Clinic Coordinating Center for Clinical Research.

The withdrawal of the selective COX-2 inhibitor rofecoxib raised questions about the cardiovascular safety of these drugs, including the

sole remaining COX-2 inhibitor in the U.S., celecoxib. A 2005 FDA advisory panel recommended conducting a cardiovascular outcome trial to clarify the relative safety of celecoxib compared with non-selective NSAIDs.

The PRECISION trial was designed with the advice and consent of FDA to address cardiovascular, GI, and renal safety of representative drugs within this class.

Now, I served on that 2005 advisory panel and we heard from Dr. Richard Platt, an epidemiologist who I think made a very important comment. He said that "Observational studies are best at finding relative risks that are more than 2. I think that I would pay some attention to relative risks of 1.5. I get very nervous about adjusted relative risks at 1.2."

Because we expected there to be relatively similar effects of these drugs, we knew that we could answer the question only with a very large longer-term randomized controlled trial and that was the setting in which we designed PRECISION.

The primary objective was a non-inferiority assessment of the cardiovascular risk of celecoxib versus two widely used non-selective NSAIDs, naproxen and ibuprofen, in osteoarthritis and rheumatoid arthritis patients.

We recognized, however, that when you do a large trial like this, you can study many other aspects of these drugs. And we were well aware of the other risks of the drugs, so we included comparative safety of celecoxib versus the 2 NSAIDs for all-cause mortality, gastrointestinal and renal adverse events and I'm going to show you all of these data.

The trial was guided by an executive committee that was multi-disciplinary that included cardiologists, gastroenterologists, and rheumatologists, and a non-voting sponsor representative. We ask all members of the executive committee to agree not to accept any payments for related work on NSAIDs from any maker of these drugs for the duration of the trial, which actually turned out to be many years.

I'd also like to acknowledge for just a moment the project manager for this trial, Lisa Wisniewski at the Cleveland Clinic, who was there from day 1, spent 10 years with us as a project manager for the trial and deserves a lot of credit in helping us get it done.

The design of the trial is shown here. We studied osteoarthritis or rheumatoid arthritis patients with established cardiovascular disease or increased risk who required NSAIDs for at least 6 months for symptom relief. We felt that equipoise would be present only if we studied people that needed these drugs on a daily basis to get through the activities of daily living.

So these were patients with significant arthritis and high cardiovascular risk. We randomized to 100 BID of celecoxib, 600 TID of ibuprofen, or naproxen, 375 BID. We provided all patients with esomeprazole, 20 to 40 milligrams, for GI protection.

We included the option for increased dosage for unrelieved symptoms to naproxen, 500 BID,

ibuprofen, 800 TID, or celecoxib BID, but please note that increases in celecoxib dosage were allowed only in rheumatoid arthritis because the label restricted use to 200 milligrams a day in osteoarthritis.

We designed the trial to run until we received 580 primary events and we required a minimum follow-up of all patients of 18 months. Now, we adjudicated endpoints and, for the non-inferiority assessment, the primary analyses used the APTC endpoint of cardiovascular death, including hemorrhagic death, non-fatal MI, or non-fatal stroke.

Other pre-specified safety endpoints included an expanded MACE endpoint that included the primary endpoint plus revascularization, hospitalization for unstable angina, or TIA. We also adjudicated a composite of gastrointestinal events, including iron deficiency anemia of GI origin, which required a 10 percent drop in hematocrit or a 2-gram drop in hemoglobin.

We adjudicated major renal events, including

hospitalization for renal failure, but the primary endpoint was an increase in creatinine and we can discuss that later. We also adjudicated hospitalization for hypertension or heart failure. We screened about 32,000 patients and we randomized a little more than 24,000 at 923 global centers beginning in October 2006.

The mean drug exposure for celecoxib was 104 milligrams BID; for ibuprofen, 681 milligrams TID; and for naproxen, 426 milligrams BID. The mean duration of treatment was 20.3 months and mean follow-up was 34.1 months. And we actually achieved 607 primary APTC events.

Now, to establish non-inferiority, the trial design required pairwise comparisons of celecoxib with the other drugs to meet 4 criteria; an upper 97.5 percent confidence interval less than or equal to 1.33 for the intention-to-treat analyses truncated at 30 months, an upper confidence interval of less than or equal to 1.4 for an on-treatment analysis truncated at 42 months.

This is defined, the on-treatment analysis,

as events occurring while the patient was taking study drug and for 30 days thereafter. For both ITT and on-treatment, we required a point estimate of the hazard ratio to be less than 1.2 for both of those. In other words, if more than 12 percent excess events were seen in any pairwise comparison, the non-inferiority criterion would have failed.

Why did we do this with an ITT and on-treatment analysis in parallel? Intention-to-treat analysis is preferred in efficacy studies because it preserves the integrity of randomization and represents a conservative assessment of benefits. However, ITT analysis can dilute safety signals by including events occurring after patients stop the therapy.

On-treatment analysis offers complementary insights (phonetic) in safety studies because it includes events occurring only while patients are actually taking study drugs.

To ensure a rigorous safety assessment, we pre-specified achieving non-inferiority using both approaches. This shows the selected baseline

characteristics of the patients in the trial. They were very balanced, as you would expect with such a large sample size.

The average age was in the early 60s. About two-thirds were female. There is a pre-disposition of women to develop osteoarthritis and rheumatoid arthritis, so that's not surprising. You can see the RA population was about 10 percent, 90 percent OA.

Between 20 and 25 percent had known cardiovascular disease. The others were high risk for disease. Prior aspirin use was stratified and I'm going to show you more about that later. And that was about 45 percent of patients. And about a third were diabetic. It was one of the enrichment factors that was used here.

This slide is probably the most important slide of the presentation. This is the primary non-inferiority analysis and I'd like to walk you through what we saw for this primary APTC endpoint. On the left, you see the ITT, the intention-to-treat analyses.

For celecoxib versus ibuprofen, the celecoxib hazard ratio was .85. The celecoxib versus naproxen hazard ratio was .93. So in both cases, there were lower rates of events with celecoxib compared to the conventional NSAIDs. This results in a non-inferiority p value of less than 0.001.

Ibuprofen versus naproxen in the intent-to-treat population also met the non-inferiority criteria. Let me also comment here that there's a color scheme used here of orange for ibuprofen, blue for naproxen, and gold for celecoxib. This color scheme is maintained throughout the entire rest of the presentation, so if you ever have any questions on a slide, orange, ibuprofen; blue, naproxen; gold, celecoxib.

Now, look to the right and you'll look at the on-treatment analyses. Celecoxib hazard ratio versus ibuprofen was .81. Celecoxib versus naproxen was .90. Again, the p value for non-inferiority was less than 0.001 for both analyses.

Please also note that ibuprofen versus

naproxen; ibuprofen just barely meets the non-inferiority criteria. The hazard ratio is 1.12. It's right on the borderline of non-inferiority. And the hazard ratio for ibuprofen versus naproxen is slightly elevated at 1.12, but it does strictly speaking meet the non-inferiority trial criteria.

Now, I'm going to show you a number of secondary safety endpoints. Keep in mind that we recognize that we could look at a lot of outcomes in this large population and we thought it would be in the public interest to do so. These secondary and tertiary safety analyses were pre-specified to provide a more complete assessment of the relative safety of these comparators.

These analyses are not adjusted for multiplicity, as is the case with safety analyses. We will present both ITT and on-treatment analyses with hazard ratios and 95 percent confidence intervals.

This is the expanded MACE endpoint, the broader major adverse cardiovascular events. Again, you see that the order is the same; highest

rates with ibuprofen, intermediate rates with naproxen, and the lowest rates with celecoxib.

The p values comparing these do not meet conventional levels of statistical significance, but I would point out that there was about a 15 percent higher rate of MACE, expanded MACE with ibuprofen, with a p value of .06, so borderline significant, a trend, if you will.

On treatment, the differences were slightly more evident. The hazard ratio for celecoxib versus ibuprofen was .82 with an upper confidence interval of .97, not crossing unity. The comparisons between celecoxib and naproxen and ibuprofen and naproxen were also not statistically different. You can see and you'll see this again and again. The on-treatment analyses tend to show bigger differences because they're looking at the people when they're actually taking study drug. So you get a little bit more clarity about differences between drugs from the on-treatment.

This is time to death from cardiovascular causes. And you will see on the left in the ITT

analysis slightly higher rates of cardiovascular death with ibuprofen and naproxen compared with celecoxib.

These differences are somewhat more striking in the on-treatment analysis where, in this case, the hazard ratio for CV death was .64 for celecoxib versus ibuprofen with confidence intervals that did not cross unity. The differences between celecoxib and naproxen and between ibuprofen and naproxen do not approach statistical significance.

This is time to all-cause mortality and you see here that, for celecoxib versus ibuprofen, for all-cause mortality, the hazard ratio for celecoxib is .92. For celecoxib versus naproxen, the hazard ratio is .80 and, again, there is about a 25 percent higher rate of all-cause mortality with naproxen that's borderline significant, with a p value of .052.

On treatment, the differences in all-cause mortality are again more striking, with the highest rates of all-cause mortality with naproxen. Similarly, with ibuprofen, note the hazard ratios

of .68 and .65, and in both cases confidence intervals that do not reach unity. The lowest rates of all-cause mortality were observed with celecoxib.

This is time to composite gastrointestinal events and you will all recall that the COX-2 inhibitors were introduced to be potentially safer from the GI perspective.

What you see in the ITT analysis is a 54 percent higher rate of composite GI events with ibuprofen, a 41 percent higher rate of these events with naproxen. The p values are significant. The hazard ratio is in the range of .65 to .7.

On treatment, the differences are very striking, with more than double the rate of GI events with either ibuprofen or naproxen compared with celecoxib. This was unanticipated. This is the time to composite renal event. On the left, you see the intention-to-treat analysis.

There was a 64 percent higher rate of renal events primarily driven by increases in creatinine with ibuprofen, with a hazard ratio of celecoxib

versus ibuprofen of .61 and a p value of 0.004.

In the on-treatment analysis, both ibuprofen and naproxen had higher rates of adverse renal events. In both cases, the upper confidence intervals do not cross unity. The lowest rates of renal events were observed in the celecoxib arm in people while they were actually taking study drug.

Now, this is a post hoc analysis and I'm going to show you a couple of post hoc analyses here. And whenever I do, I will tell you that it is a post hoc analysis for your edification. But we thought it would be useful to show you this composite.

This is any of the adverse outcomes that we looked at in PRECISION. And so you see any adjudicated cardiovascular, GI, or renal event. These events were 28 percent higher with ibuprofen with a number needed to harm of 59. They were 15 percent higher with naproxen, with a number needed to harm of 117. In both cases, these are statistically significant.

Notably, there is also a difference here

between ibuprofen and naproxen with a statistically significant p value.

On treatment, once again, you see more evident differences between ibuprofen again in orange, naproxen in blue, and celecoxib in gold with greater rates of adverse events across the spectrum of adjudicated events.

Now, we also collect investigator-reported adverse events and this is supportive data that helps us to test whether or not the investigators are seeing the same things that we are seeing.

You will note here that anemia was more common in the ibuprofen and naproxen arms, substantially more common than with the celecoxib arm, perhaps not surprising given the GI effects. You'll see that investigators reported increased blood pressure more often with ibuprofen than the comparators. You'll note that with both ibuprofen and naproxen there were higher rates of reports of hypertension by investigators and very notably, with ibuprofen, there were higher reports of increased creatinine noted with ibuprofen compared

with either celecoxib or naproxen.

Now, the effects on blood pressure were of considerable interest. And so we designed as part of PRECISION a dedicated ambulatory blood pressure substudy. Particularly for the cardiologists here, ambulatory blood pressure studies are considered the gold standard for evaluating blood pressure effects of drugs.

This was published in the European Heart Journal by some of my colleagues. And it shows what happens to blood pressure in a substudy, a dedicated substudy of PRECISION. This was pre-specified. It was performed in 444 patients at 60 U.S. centers. Ambulatory blood pressure was measured every 20 minutes during daytime and every 30 minutes at night.

The primary endpoint was the change from baseline in 24-hour mean systolic blood pressure at month 4. A post hoc analysis compared the percentage of normotensive patients, those that had blood pressures less than 130 over 80, who became hypertensive at month 4.

Here is the 24-hour blood pressure change for naproxen with baseline shown in blue and 4 month in gold. Please note that the difference was modest, 1.58 millimeters higher with naproxen. But also note the blunting of the night dipping response, which has been strongly linked to adverse cardiovascular outcomes. So night dipping is blunted by naproxen, but the overall change is relatively modest.

Here's the 24-hour ambulatory blood pressure for ibuprofen. It's a 3.65-millimeter increase. It's consistent throughout the day and with a more dramatic blunting of the night dipping response in blood pressure.

Then finally, celecoxib, 24-hour blood pressure; the mean change was minus .26, essentially 0, and the curves are pretty much superimposable between baseline and 4 months.

Let me summarize and show you the statistical measures. Comparing ibuprofen to celecoxib, there was about a 4-millimeter net difference in blood pressure that was significant

with a p value of less than 0.001.

The other differences between comparators were not statistically significant, but this 4-millimeter difference in blood pressure was the principal important finding from the ambulatory blood pressure study.

Then lastly, I want to remind you that this is a post hoc analysis. We did look at normotensive patients developing hypertension. It occurred in 10.3 percent of the celecoxib patients, 19 percent of the naproxen patients, and 23.2 percent of the ibuprofen patients.

Those differences between celecoxib and the non-selective NSAIDs were statistically significant. It's also in the European Heart Journal manuscript. And then finally, since we adjudicated hospitalization for hypertension, we had a chance to look to see. This is now in the main PRECISION trial.

This is a pretty interesting endpoint in that it's blood pressure increases enough to get you in the hospital and it was 69 percent higher

with ibuprofen. It was not statistically different between celecoxib and naproxen in the ITT population, nor was it in the on-treatment.

But again, if you look at the hazard ratio for hospitalization for hypertension in the celecoxib versus ibuprofen arm, the hazard ratio is .58 and the confidence intervals are essentially statistically significant.

Now, I'd like to now, having shown you the main results, address four critical questions that I think are perhaps going to be fodder for discussion during the course of the next day and a half.

Could retention and treatment discontinuation rates have meaningfully influenced the primary outcome analyses of the trial? I want to address that. Did potential interference of ibuprofen or naproxen with the beneficial effects of aspirin explain the primary findings of the study.

Number three, did the trial evaluate comparable doses of celecoxib, ibuprofen, and

naproxen? And lastly, are the results of PRECISION consistent or inconsistent with the CNT meta-analysis?

Let me talk about adherence and retention. The trial academic leadership was aware that previous pain trials, even short-term studies, had lower than optimal adherence and retention.

Patients with unrelieved pain, as our rheumatologists kept reminding us, become frustrated and withdraw at high rates from pain trials. By design, we included pathways to manage disease flares, including TENS, tramadol, low-dose opiates, intra-articular steroids, or hyaluronic acid, and others.

When we observed higher than desired rates of non-retention, we engaged in multiple initiatives for both the investigators and patients to do everything we could to keep as many patients in the trial for as long as we could.

But this was a challenge. As a cardiologist, we are used to doing trials where we keep 99 plus percent of the patients in for the

duration of the trial and the history of pain trials is quite different.

This is what actually happened with retention. We kept 91 percent of the patients in for 12 months, 89 percent for 18 months, 81 percent at the time of ITT analysis, and 73 percent at the time of on-treatment analysis.

This is the rates of drug discontinuation. It ranged from 37 percent discontinuation at 12 months to 69 percent by the 42-month on-treatment analysis. Now, we look back at the other studies that compared NSAIDs with coxibs. And what we saw was, every study in this space has had similar troubles.

For example, in the MEDAL trial, they compared etoricoxib and diclofenac. At 36 months, non-adherence, patients discontinuing the drug, was 81 percent and non-retention was actually 53 percent.

You see high rates in the TARGET trial as well. Our rate of non-retention of 11 percent at 18 months and 19 percent at 30 months was actually

somewhat more favorable than others had achieved. Nonetheless, we really sought to keep as many patients in as we can.

I'm going to show you some analyses later that perhaps help us understand whether this might have impact on the results of the trial.

Let me first tell you that the characteristics of the non-adherent patients were essentially balanced across the treatment groups. We thought this was important to look at because, clearly, these patients were different who were stopping study drug across the trial. That would be informative.

Similarly, this table -- and you can read these on your own; I'm not going to walk you through it -- were characteristics of non-retained patients. And again, they were very, very similar across treatment arms.

Essentially, there does not appear to be major differences in who was not retained in the trial. Now, we performed a sensitivity analysis imputing potential missing events. But when we saw

the FDA analysis, we thought the FDA statisticians did a better job.

So I'm going to show you the analysis from the FDA statisticians. These are the numbers of primary events in the first row and the pairwise comparison hazard ratios of .86 and .94. This is from the FDA.

Subjects who withdrew are shown here. You can calculate based upon the percent of exposure achieved. We achieved about 90 percent of the potential exposure. Or it was really 89 percent. So you can then calculate the likely number of events that were missed.

You can then look and see how imbalanced would missing events have to be in order to tip the analysis toward inferiority. And so what you see is you'd need 59 additional events with celecoxib versus 20 with naproxen. You would need 80 with celecoxib versus 22 with naproxen to reach that tipping point.

What the FDA statisticians said -- and our analysis parallels this exactly -- is, in order for

the upper bound of the 95 percent confidence interval, for the odds ratio to exceed 1.33, the imputed number of events in the celecoxib arm would have to be 3 times as large as in the naproxen arm and 4 times as large as in the ibuprofen arm.

So we think that it really would be very difficult to believe that there is any imputation here which would result in not achieving the non-inferiority endpoint.

So in summary, for adherence and retention, we did see similar rates of non-adherence and non-retention across the 3 treatment groups. The baseline characteristics were similar across treatment groups for non-adherent and non-retained patients.

On-treatment analyses become useful here because we wanted to see whether or not, while people were actually taking the study drugs -- we know those people then obviously have been retained -- did we have similar non-inferiority? In fact, they reinforced the ITT results.

Finally, sensitivity analyses evaluating

potential effects of missed events show that, even in extreme imbalance disfavoring celecoxib cannot change the non-inferiority inclusion.

Now, we heard a lot this morning about aspirin and we recognize that this was an issue we needed to evaluate. And so the question is, did the potential interference of ibuprofen or naproxen with the beneficial effects of aspirin explain the primary findings of the study.

I want to talk about this in some detail because it was obviously a very important topic for this morning. The potential interaction between aspirin and ibuprofen or naproxen have been described in the platelet function laboratory.

However, actual clinical effects of this theoretical interaction have never been adequately verified in a randomized clinical trial. This is all based upon platelet function measures, not clinical outcomes.

For ethical reasons, we could not randomize to aspirin, but we did stratify for aspirin use. Patients with existing cardiovascular disease, we

couldn't withhold aspirin, so we couldn't randomize. The best we could do would be to stratify, which we did.

This approach provided the opportunity by stratifying to examine whether the theoretical NSAID platelet function interaction actually affected major cardiovascular outcomes. On the left, you see, again, same color code by treatment group; about 45 percent of the patients in all 3 groups were taking aspirin at baseline.

Almost all of these actually remained on aspirin at the end of the study. There were a few patients that dropped into aspirin, just about 4 percent. So essentially, the consistency of aspirin across the trial was very high.

Now, I want to talk with you about what we would have expected based upon the theoretical interaction. So the top panel is about what the theory might have proposed. You see from the CNT meta-analysis that celecoxib versus ibuprofen was essentially believed to be neutral.

If ibuprofen was interfering with aspirin

efficacy, then it would confer an advantage to celecoxib and it should move the hazard ratio toward a more favorable hazard ratio for celecoxib, resulting -- and I show you theoretically an interaction p value that would be statistically significant.

What we actually saw was no interaction and, if anything, it trends in the opposite direction, that this biomarker, this platelet function biomarker, in this simple analysis does not translate into a clinical effect.

In fact, if anything, it's pointing in the opposite direction, but this is simple interaction testing and we wanted to go deeper. And so one of my colleagues and I did an analysis that appeared two weeks ago in the Journal of the American College of Cardiology, where we did a propensity-weighted, propensity-adjusted analysis to provide a more sophisticated look at what happens with and without aspirin.

Let me show you first expanded MACE. Now, the right-hand panel shows you what happens in the

patients that did not receive aspirin. And this is a test of the inherent effects of the drugs in the absence of co-administration of aspirin, highest rates with ibuprofen, intermediate with naproxen, lowest with celecoxib, very similar to the results of the trial that we showed earlier.

In the presence of aspirin, instead of seeing a widening of differences between the treatment arms, we actually see a narrowing. This is the opposite with what would be predicted if there is actually an interference by ibuprofen or naproxen with the efficacy of aspirin.

Let me show you additional endpoints. This is the GI outcomes. Without aspirin on the right, there is a threefold higher, approximately a threefold higher rate of GI outcomes with ibuprofen and naproxen compared with celecoxib.

When you give aspirin, you narrow that advantage to about twofold. And so again, here, the results are consistent. You don't see evidence, compelling evidence of an interaction. This is renal outcomes. And in the absence of

aspirin for renal outcomes, you see higher rates with naproxen and ibuprofen.

Again, this is a test of the inherent effects of the NSAID being studied in the absence of aspirin and, rather than seeing a widening of those differences, when aspirin was present, if anything, you see a little bit of narrowing of those differences, again showing no clinical evidence of an interaction.

Then this is a composite, so this is cardiovascular, renal, and GI safety. In the absence of aspirin, this is really a test of the relative effects of these drugs without aspirin. Ibuprofen has the highest rates, naproxen intermediate, and celecoxib the lowest, highly significant p values.

In the presence of aspirin, those differences do not widen. They narrow. These data do not show evidence that these theoretical biomarker measurements of platelet function are actually translating into an observable clinical effect in the PRECISION trial.

The next question I want to address is, did the trial evaluate comparable doses of celecoxib, ibuprofen, and naproxen? Now, as I pointed out earlier, we were limited by regulatory labeling in the OA patients to the 200 milligrams of celecoxib.

So why should the issue draw our attention? In the CONSORT diagram that we published in the New England Journal of Medicine, we showed the withdrawals for insufficient clinical response, which occurred in about 8.5 percent of the naproxen and ibuprofen patients and about 1 percent absolute difference higher rates with celecoxib that was statistically significant, just a little bit higher with celecoxib.

In the next two slides, I'm going to show you four additional measures of the efficacy of these drugs for their intended indication in PRECISION. On the left is the visual analog pain scale. It's a 100-millimeter scale. And you can see in parallel, all three drugs, significantly reduced pain perceived by the patient using the VAS scale.

It turns out, in this analysis, naproxen is slightly better than ibuprofen or celecoxib. Ibuprofen and celecoxib are virtually indistinguishable here, so a slight advantage for naproxen in the trial, in the visual analog pain scale.

On the right, you see the Health Assessment Questionnaire Disability Index. And in this case, again, very similar effects across the three drugs. I should point out, on the left panel, that the very small difference of about a half a millimeter on the 100-point scale is actually an order of magnitude smaller than the difference that's considered to be clinically significant.

So fundamentally, these are very, very similar efficacy measures in terms of the pain relief. We also did a global assessment of arthritis and, again, these are all defined in the manuscript. And you see here again very similar results, parallel effects of the three drugs.

Naproxen was slightly better here with a nominally significant p value versus celecoxib.

Celecoxib and ibuprofen were very similar.

Then finally, on the right, we think this is actually an important analysis. Because we had all these rescue medications, we could track who was needing a rescue medication and they were the same across treatment arms; actually in this case, slightly higher with naproxen than the other agents. Keep in mind that the overall efficacy is the effect of the NSAID and the effect of the rescue medication.

So again, this can maybe color the results a little bit. So what do we see on dose? For osteoarthritis patients, 90 percent of the study population, maximal approved doses are celecoxib, 200 milligrams daily, ibuprofen, 3,200 milligrams daily, and naproxen, 1,500 milligrams daily.

The average achieved dose as a proportion of the maximal allowed doses were 100 percent for celecoxib, 64 percent for ibuprofen, and 57 percent for naproxen. We believe that, if maximal therapeutic doses of ibuprofen and naproxen had been used, their adverse effects on blood pressure,

renal function, and GI toxicity would likely have been even more apparent. The doses achieved were clinically relevant and generally comparable based on multiple different efficacy analyses.

Now, finally, how do the results of PRECISION inform us in the setting where there exists a pre-existing large meta-analysis?

I personally believe that a single large well-performed trial is more compelling than meta-analyses because meta-analyses often have a lot of heterogeneity. You can see that the CNT direct comparisons would indicate a proximate neutrality between celecoxib and ibuprofen and between celecoxib and naproxen for the APTC for major adverse cardiovascular events.

PRECISION shows very similar results, but please note the width of the confidence intervals. PRECISION is much more precise in giving us an answer here. Look at the confidence intervals from CNT. They go from about .5 to about 2.

So PRECISION provides us -- and that was one of the reasons we chose the name -- a more precise

reflection of the relative effects on the cardiovascular outcome for these three drugs with much narrower confidence intervals, but relatively similar point estimates.

So what are the major conclusions from PRECISION? We saw numerically fewer APTC events with celecoxib and we met all four non-inferiority criteria by a large margin. In the ITT analyses, chronic treatment, again with prescription doses of ibuprofen, not over-the-counter doses, compared with celecoxib was associated with higher rates of gastrointestinal and renal adverse events and higher rates of hospitalization for hypertension.

In the on-treatment sensitivity analysis, ibuprofen showed higher rates of MACE, cardiovascular death, all-cause mortality, and major gastrointestinal and renal events. What about the naproxen comparison? Numerically fewer events with celecoxib by a wide margin, meeting all four non-inferiority criteria in the ITT analysis, chronic treatment, again with prescription doses, not over-the-counter doses, compared with celecoxib

was associated with higher rates of GI adverse events and a borderline significant increase in all-cause mortality.

In the on-treatment sensitivity analysis, naproxen showed higher rates of all-cause mortality and major gastrointestinal and renal events.

We have a few additional conclusions to share with you. The findings challenge the widely held view that naproxen provides superior cardiovascular safety. Adherence and retention were lower than typical cardiovascular outcome trials, but similar to other NSAID pain studies with no strong evidence for an effect on the primary non-inferiority findings.

The dosages used in the trial provided similar anti-arthritic efficacy. Results were consistent regardless of aspirin administration, although aspirin, if anything, narrowed the advantages a bit for celecoxib.

Clinically meaningful differences and effects on blood pressure represent a potential factor in differences in cardiovascular outcome. 4

millimeters of mercury, epidemiologists will tell us is potentially significant.

A few more conclusions; very important, we studied the relative safety of three drugs and not the more than 20 other currently marketed NSAIDs. There's only so much you can do in one trial.

We may not make any direct inferences regarding the effects of NSAIDs compared with placebo. We could not for ethical reasons have a placebo arm. So we are not telling you, with any of these drugs, what their safety is relative to placebo. We're telling you what the effects are relative to each other.

These data do not provide conclusive evidence regarding the safety of intermittent treatment or use of low-dose over-the-counter preparations. We don't have an answer to that question based on PRECISION.

The academic leadership of the trial does believe that PRECISION suggests a strategy for these patients. For arthritis patients who require NSAIDs to achieve acceptable quality of life,

particularly those at high cardiovascular, GI, or renal risk, the PRECISION trial suggests that a clinical strategy of starting patients on celecoxib, 200 milligrams daily, may be the safest approach, reserving full therapy doses of ibuprofen and naproxen for patients who do not respond to celecoxib.

The full manuscript and supplement are available and has greater details on exactly the endpoints, and adjudication, and so on, and you're certainly welcome to read it.

I'm going to leave you with one final thought. After withdrawal of rofecoxib, many observers assumed that all COX-2 inhibitors increased major adverse cardiovascular events. Existing randomized trials were small and relatively short in duration. This point did not get made well enough earlier.

We're talking about handfuls of events in those comparisons prior to PRECISION, very small numbers of events. Observational studies and meta-analyses showed inconsistent results with relative

risks typically in the range of .8 to 1.2.

The PRECISION trial demonstrates the importance of determining the risks and benefits of therapies based upon randomized trials rather than theoretical considerations. The findings highlight differences in outcome that appear related to multiple pharmacological effects of these drugs, not necessarily their COX-1 versus COX-1 selectivity.

Thank you very much for your attention.

Applicant Presentation – Stanley Cohen

DR. COHEN: Good morning. I'm Stanley Cohen. I'm a clinical rheumatologist from Dallas, Texas and also a clinical trialist. And I served as an investigator in this protocol. It's my great pleasure to be here today and I'm here on behalf of the sponsor as a consultant.

I appreciate the opportunity to provide a few remarks on my thoughts on this dataset and the implications for treatment because, frankly, rheumatologists and our primary care colleagues are the ones who treat these patients and every day

face the treatment decisions about the pros and cons of use of these therapies.

Before talking about the dataset, I'd like to briefly give you an overview of the diseases that we manage and were studied in this trial. Rheumatoid arthritis, as we know, is a chronic inflammatory systemic autoimmune disease; occurs in about 1 percent of the population. Age of onset is between 40 and 70 years of age in general, although any age can be affected; two-thirds women; and if not treated early and aggressively, is associated with significant disability.

It's accompanied by multiple other co-morbidities, serious infections, lung cancer, lymphoma risk is increased; and we know there is an increased risk of cardiovascular events in these patients. And there's been a world of data in the last decade or so demonstrating the role of inflammation and leading to the atherogenic process.

The cornerstone of management for patients with rheumatoid arthritis disease-modifying anti-

rheumatic drugs; we are blessed now in the 21st century to have wonderful targeted therapies that have greatly improved patient outcomes in rheumatoid arthritis, relegating NSAIDs in this population to more of an adjunctive therapy for short-term symptomatic relief.

Osteoarthritis is far more common than rheumatoid arthritis and, according to the CDC in 2018, 30 million U.S. adults have osteoarthritis. Again, all ages can be impacted, but more common as we age; most common in people over 65 years of age.

Common risk factors include aging, obesity, previous joint injury, joint overuse, weak musculature, and certainly genetic predisposition. The lifetime risk of developing symptomatic knee OA is approximately 40 percent in men and 50 percent in women. And the risk rises to 60 percent in those with elevated BMI.

One in 12 people over 60 years of age have hand osteoarthritis. Osteoarthritis is primarily characterized by chronic pain with limitation of physical function. So in this study, 90 percent of

the patients who studied had osteoarthritis. And I think that's a relevant population to study when considering NSAID safety.

The treatment of osteoarthritis, as I mentioned, is focused primarily on the management of symptoms. We have no disease-modifying therapy unfortunately. So the long-term management consists of long-term treatment of anti-inflammatories or analgesics.

We do everything we can to get the patients to lose weight and also to strengthen their muscles, and reduce stress on their joints, and learn proper exercise.

So what do we have as far as pharmacologic treatment? The primary treatment again remains NSAIDs, but be aware that we have not had any new oral therapies for osteoarthritis in the last 17 years, no new therapies for our patients. Their options are limited.

NSAIDs do ease inflammation-related pain and are the mainstay of treatment. We do use analgesics, acetaminophen. The literature there is

somewhat controversial. We certainly try that in the patients with less severe disease. Tramadol is used quite frequently and opioids have been the default medication as well for people with severe chronic pain.

With the concern over NSAIDs that has been discussed here today over the last 15 to 20 years, the utilization of opioids increased tremendously and probably played a significant role in the crisis we're having now about opioid utilization.

Corticosteroids, intra-articular corticosteroids do provide short-term benefit. There is no role for oral corticosteroids in osteoarthritis. Intra-articular hyaluronans are available in the clinic and we use them, although the effect size of these therapies are modest.

So let's take a look at celecoxib for osteoarthritis. I just want to remind the group about some of the clinical trial data that led to the approval of celecoxib in some of the studies that were conducted. So this was a study, a 12-week study with primary endpoint at 12 weeks,

looking at the WOMAC composite score and the OA severity index in patients with osteoarthritis of the knee.

The Y axis is the mean change from baseline. And this was a dose-ranging study looking at celecoxib, 100 milligrams BID, 200 milligrams BID, or naproxen, 500 milligrams BID in comparison to placebo.

You can see that, for both outcomes, celecoxib and naproxen were superior to placebo. But I do want to point out here that there was really no dose response for celecoxib in osteoarthritis in this particular study. Both the 100-milligram and 200-milligram BID doses of celecoxib achieved similar clinical benefit.

A subsequent study looking at a much larger population of patients, nearly 1,000 patients looking at the WOMAC pain score and the WOMAC physical functioning score at week 12; again the primary outcome. Again, demonstrated statistical superiority of celecoxib and 100 milligrams BID and 200 milligrams BID compared to placebo, as did

naproxen, 500 milligrams BID.

Again, I want to point out the lack of a dose response here, which led to the approval of the 200-milligram dose in osteoarthritis and 200- to 400-milligram dose was approved for rheumatoid arthritis due to some differences in outcomes in the RA population.

So Dr. Nissen addressed a number of the questions in adherence and retention therapy, the aspirin interaction, as well efficacy of celecoxib at the 200-milligram dose. Again, just to remind everyone, this was a very large safety study. I certainly applaud the steering committee and probably the rheumatologists on the committee who had input and looking at some outcomes of efficacy to have some understanding.

Again, this is data similar to what Dr. Nissen showed but broken down for the OA population and the RA population, again looking at change in pain as measured by VAS scale. And you can see similar improvements in pain for the osteoarthritis and rheumatoid arthritis

populations, with some statistical difference that I'm not sure is meaningful from a clinical significance.

But again, a number of things were looked at to measure efficacy in this study, which primarily was a large safety study. So to me, the main findings of the PRECISION trial was, this was primarily a study of osteoarthritis, which is very important to us who see patients daily for guidance and insight in how we manage these patients.

Dr. Nissen mentioned the maximal approved doses of celecoxib, ibuprofen, and naproxen and that the doses for celecoxib were 100 percent of the maximal dose versus 64 percent and 57 percent for ibuprofen and naproxen respectively.

At the doses used in the PRECISION trial, OA patients treated with celecoxib experienced similar relief from pain and did not have higher cardiovascular risk than patients treated with ibuprofen and naproxen.

However, at these doses, patients treated with celecoxib were likely to experience less

toxicity related to blood pressure, renal function, and GI bleeding.

So what are the take-home messages to me, the implications for treatment? In the clinic, we know when we select a treatment that's intended to alleviate the symptoms of chronic disease, both the providers and the patients desire a treatment that is best tolerated as long as it can be reasonably expected to achieve therapeutic goals in a large proportion of patients.

Based on the results of the PRECISION trial, in patients with osteoarthritis, treatment with celecoxib, 200 milligrams daily, can be expected to achieve clinically meaningful pain relief without an increase in cardiovascular risk and with a likelihood of less GI and renal toxicity when compared to the doses of ibuprofen and naproxen that were studied. Thank you.

Applicant Presentation – Milton Pressler

DR. PRESSLER: Thank you, Dr. Cohen, for your insights on the impact of these medicines to patients with arthritis.

For arthritis patients, PRECISION provides important information on the safety of celecoxib, ibuprofen, and naproxen. Let's recap some key points.

PRECISION was a large clinically relevant trial of currently used drugs in practice. It is highly representative and generalizable to patients with chronic arthritis pain, who are largely those with osteoarthritis. The trial studied approved and clinically relevant doses of celecoxib versus doses of 2 non-selective NSAID comparators, naproxen and ibuprofen.

PRECISION was carefully designed. Non-inferiority criteria were pre-specified and rigorous. And the findings are unaltered by considerations of missing data. Aspirin use did not show a significant interaction with the outcomes. PRECISION's applicable to long-term prescription use, not short-term, over-the-counter use of NSAIDs.

The trial demonstrated robust and consistent results across pre-specified and post hoc analyses

to answer the questions that were posed.

PRECISION greatly expands the clinical trial safety database for celecoxib. It's one of the largest randomized arthritis studies of clinical outcomes to date and was prospectively designed to measure cardiovascular outcomes with NSAIDs.

It included more than 24,000 patients. It utilized blinded adjudication, a pre-defined APTC, GI, renal, hypertension, and congestive heart failure outcomes. It embedded a substudy to precisely measure blood pressure changes by ambulatory blood pressure monitoring.

The total follow-up in PRECISION was over 68,000 patient-years, over 45,000 patient-years for the celecoxib versus ibuprofen comparison, and over 45,000 patient-years for the celecoxib versus ibuprofen comparison.

In contrast, the CNT meta-analysis of prior randomized controlled trials of NSAIDs, the follow-up was approximately 31,000 patient-years for all 5 coxibs versus naproxen and around 11,000 patient-years for all 5 coxibs versus ibuprofen.

Let's review the situation as it stands today in 2018 with what we knew prior to PRECISION in 2014. The findings in PRECISION are consistent with prior knowledge on safety. The findings are fully consistent with the results of the direct comparisons in the CNT meta-analysis for the doses used of celecoxib, naproxen, and ibuprofen in patients with osteoarthritis.

It provides substantial evidence on the cardiovascular safety profile of 200 milligrams of celecoxib a day, the clinically relevant dose for patients with osteoarthritis.

The effects in the trial are not influenced by concomitant treatment with aspirin. It provides important insights into changes in blood pressure and renal function at the doses studied of celecoxib, naproxen, and ibuprofen.

It supports a more favorable gastrointestinal safety profile of celecoxib at the doses studied as compared to two non-selective NSAIDs, even with concomitant treatment with a proton pump inhibitor, esomeprazole.

Physicians should be made aware of these results. In conclusion, celecoxib continues to demonstrate a favorable benefit-risk profile for treatment of patients with arthritic pain, especially for those with osteoarthritis.

The results of PRECISION should be included in the United States package insert. PRECISION provides robust and important information on cardiovascular safety to guide prescription use of clinically relevant doses of celecoxib, naproxen, and ibuprofen.

So considering this, in appendix 11 of the briefing book, Pfizer outlines the changes proposed for the Celebrex USPI. We proposed to add a description of PRECISION's study design, and then the population, and doses, and drugs tested, and the principal findings.

The principal findings include, over a mean follow-up of 34 months, celecoxib met 4 pre-specified non-inferiority criteria, thus demonstrating no greater risk for cardiovascular events than naproxen or ibuprofen at the doses used

in the study.

We look forward to working with the FDA to achieve the right level of detail. Thank you for your attention. Pfizer and Drs. Nissen and Cohen welcome your questions.

Clarifying Questions

DR. NEILL: Thank you. We have approximately 30 minutes for clarifying questions. I've already got one. I see Dr. Roumie, Dr. Farber, Dr. Oliver, Warholak. Let's begin with Dr. Lewis. And if I've not mentioned your names, please keep your hands up until I get your names.

DR. LEWIS: Dr. Lewis. I have two questions and they're both in regards to the design of the trial. One question I have, I think a question highly relevant to prescribing physicians and to the general public who will be exposed to Celebrex is a dose question.

A hundred milligrams twice a day; is the label dose for OA? You should have some evidence why that was chosen. However, this was a study where you had the opportunity to better inform us

about the potential cardiovascular and other toxicities of higher doses of Celebrex for which you can prescribe them for pain, dysmenorrhea, a variety of things.

Can you explain, because it was a study, why you didn't at least give the opportunity for investigators to escalate the dose of Celebrex in the 90 percent of patients enrolled with OA so that we could get information on this important question. And then I have a second question.

DR. PRESSLER: Milton Pressler, Pfizer. First of all, this was a phase 4 study and we were evaluating the doses that were approved in the two arthritic populations.

That said, we did test whether the treatment by dose had any effect on the primary outcomes and it did not. But your question has to do a lot more with the design, so I'd like to invite Dr. Nissen to expand upon that.

DR. NISSEN: I think you have to put yourself in the context of where we were in 2005, 2006. We had just gone through a very difficult

period, lots of public attention, Congressional hearings about the safety of these drugs.

To use an unapproved dose in that setting, particularly when we had some signals that suggested something happened here that I think is important for everybody to understand. Why were these very high doses of celecoxib even tested in the earlier trials?

The reason was that, in trying to establish GI safety, it was felt by another division of the FDA that celecoxib should have to be shown to be less GI toxic, even at supratherapeutic doses. And the idea was to have a conservative assessment.

There was really no thought process in that about whether that would increase cardiovascular risk. So this 800-milligram dose that was used in some of those earlier trials was a supratherapeutic dose. We simply did not think we could get investigators, IRBs, and others to accept giving supratherapeutic doses of celecoxib.

Would it have been interesting to have tested it now in retrospect? Yes. I think, in the

context of 2005, 2006, it was just not possible to do a trial at supratherapeutic doses.

DR. LEWIS: Can I follow up on what you said?

DR. NISSEN: Please.

DR. LEWIS: So 200 BID is not supratherapeutic. It's in your label, I mean, given for other things and I don't know why it's there for those other things and what the evidence was. So you may enlighten me.

But certainly at that time, another very strong feeling was that Celebrex was just sort of Vioxx Light, if you will, and that it was a dose effect. So I think, at the same time, there was certainly a concern about that. And would you favor us saying we should just change the label so everybody can only get 100 BID because we don't know about the safety of this other dose?

DR. NISSEN: First of all, my job here is not to tell all of you how to label these drugs. Honestly, what I wanted to do was to provide you with a very kind of neutral description of what we

saw in the trial. And I think you guys are going to have to have a discussion about how you feel about it.

But let me just make one more really critical point. We reviewed the efficacy data when we were designing this trial and, if you remember the slide that was shown by Dr. Cohen, there was absolutely no difference in OA patients between 100 milligrams BID and 200 milligrams BID.

We did not believe that there was evidence that we would achieve greater efficacy. And so to us, it made very good sense to study what we thought was the clinically relevant and approved dose of the drugs. Now, we can all talk about what would have happened had we done something differently.

I just don't think we could have sold to people the idea of giving very high doses in the setting that we were in.

DR. LEWIS: Then my second question about the design is two statistical questions. In your paper, you say they were stratified to aspirin, but

that the methodologies statistically to do that was post hoc, so I'm not sure I understand why that was the case.

Then you were very interested in all these other outcomes, but there was no statistical hierarchical plan that would have allowed you to make much stronger statements about them.

DR. NISSEN: Yes, and that was, in fact, by design. And when one does a trial to establish efficacy; in your space, renal; you want to determine whether an ARB reduces renal toxicity. Well, you define a series of stepdowns for hierarchy for efficacy that's never been done in safety trials.

In fact, FDA has commonly labeled safety findings, even when they weren't pre-specified. And our recently SGLT2 inhibitor was labeled for increased amputations because it was observed in the trial.

So safety findings are typically not defined in some statistical hierarchy. Efficacy claims are. And so it was just a difference in what we

were really trying to do with the trial.

DR. HERTZ: Hi, this is Sharon Hertz. I would just like to make a small correction. When we are looking at efficacy studies and we find safety issues, we may label them, but this was a dedicated safety study and there was a statistical plan. And that isn't a reason why it was okay to have hundreds of p values with no hierarchy and assume that they had some meaning.

DR. PRESSLER: Milton Pressler, Pfizer. I just wanted to clarify something. The analysis based on the strata was pre-specified. It was the additional analysis that Dr. Nissen is showing that was post hoc. The analysis based on strata of aspirin was pre-specified.

DR. NISSEN: Let me make sure that's right. So the paper that appeared in JACC which involved the propensity-weighted analysis was a post hoc analysis. But the stratification and then the look at aspirin that I showed you, the first slide that I showed you was in fact a pre-specified analysis.

DR. LEWIS: Thank you.

DR. NEILL: Dr. Oliver? And Dr. Roumie?

DR. ROUMIE: Christianne Roumie. This question is for Dr. Nissen. Can you please clarify your modified intention-to-treat analysis? You report that it accounted for those who remained on drug after randomization. Can you please speak to the crossover or drop-in groups? And were they in the modified intention-to-treat or how were they analyzed?

DR. NISSEN: Yes, so we have a slide that will show you the cross-ins. Our DMC monitored cross-ins very carefully and we got regular reports on that. And we're going to show you actually what the rates of cross-ins were in the trial. And it's a very important question for sure. So give us a second to find the slide.

Yes. So let's put that up. So there we go. So while on treatment, you can see cross-ins were about 9 percent. And at any time in the study, they were 15 percent. And the mITT analysis or the on-treatment analysis would be 9 percent of the people actually were taking one of these three

agents. Presumably, they were getting it on their own, but we were recording that.

So that shows you the analysis. Now, I'm going to ask our statistician, Kathy. How do we treat that in the trial?

DR. WOLSKI: Kathy Wolski, biostatistician at Cleveland Clinic. So for the ITT and for the mITT analysis, we did not consider these in the analysis. We did look at this after the fact in a sensitivity analysis and basically found the same result. I mean, this did not influence at all the primary result.

DR. ROUMIE: So just perfectly clear; the 10 percent of people who have crossed into, say, Naprosyn, were not analyzed in that group, but remained in their intention-to-treat group?

DR. WOLSKI: That's correct.

DR. NEILL: Dr. Farber?

DR. FARBER: I'm wondering if anybody has looked into or thought about the possibility of the vascular effect of these drugs, given the lack of the actual effect on platelets. It seems that a

vascular effect would sort of tie everything together, including blood pressure increases, cardiovascular events, renal events, et cetera. I wonder if that's been looked into.

DR. PRESSLER: This is Milton Pressler, Pfizer again. In this study, we did provide some information on blood pressure. So the substudy that was done, ambulatory blood pressure monitoring, was embedded within the overall trial to look at whether pressure effects of the drugs might also be a factor in what we were seeing.

We examined in that small group whether the changes in blood pressure were correlated with the outcomes of the patients that were in that group. And the answer is, no, there were just too few events.

But if you took changes in systolic blood pressure, per se, that were measured in the clinic and tried to correlate them with the events that we're seeing, then we did see some correlation.

Again, that's a post hoc analysis, trying to understand more about our data. Now, I'm not a

renal scientist. We have renal scientists here on the panel. But these drugs have effects on the kidney and they may have differing effects on the kidney. And kidney is very important for how blood pressure changes occur, so there may be some relationship there.

DR. NEILL: Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. Actually, my question was asked and answered with regards to crossover.

DR. NEILL: Great. Dr. Warholak?

DR. WARHOLAK: My questions are for Dr. Nissen. On slide 9, you give us an idea of what the mean daily dose is for each of the groups, but we don't have a standard deviation or range and wanted to see if you have that information.

DR. NISSEN: We can see. Do we have that? Can somebody come up with that slide? We'll certainly try to get that for you.

DR. WARHOLAK: Great. And then I must have missed it when I was reading the briefing packet, but you mentioned that you did a propensity score

analysis and I don't know which slide it was, but can you tell me which one you did and what variables you included?

DR. NISSEN: Yes. Do you have that slide? I actually had included it in my presentation and took it out. Now, we used inverse probability of treatment weighted scores and we had a very large collection of variables that we did that for.

Here we go. Yes. So let's show that slide. So let's see. There's means and standard deviations for you there.

DR. PRESSLER: So this is of the 104 twice daily.

DR. NISSEN: So you see it. Yes, so you see for overall RA and OA and for each of the three drugs, so there's your standard deviations. So we had a slide in an earlier version of my presentation that had the inverse probability of treatment-weighted analysis and we just, in the interests of time, didn't show that.

But if we can find that, that would be really great, but we may have to find it after the

break. I have it on my computer.

DR. NEILL: Thanks. So I have in order next Dr. Blaha, Dr. Ho, Rosenberg, Cunningham, Richards, Ohman, Tchetgen Tchetgen, and Schmidt. So Dr. Blaha?

DR. BLAHA: Yes, straightforward clarifying question for Dr. Nissen on MN-30, on slide 30; just I know this was a relatively minor side, but interesting; adjudicated hospitalizations for hypertension; can you just give us a sense of how is the hospitalization for hypertension adjudicated? What does that look like?

DR. NISSEN: We'll have to go back and pull out our adjudication manual. We can certainly do that. I'm not sure I can get that to you.

DR. BLAHA: Is the primary reason for hospitalization, I guess, hypertension, hypertensive emergency?

DR. NISSEN: Yes, that's the spirit of what was done, but the precise definitions; there's a manual that's used by the adjudication center. And we can pull up their definitions for you and we'll

provide that to you as soon as we can pull that up for you.

DR. NEILL: Dr. Ho?

DR. HO: I had a question related to aspirin. So in general, what type of formulation was used? Was it the immediate release versus enteric coated? And then how was aspirin use assessed over time during this study?

DR. NISSEN: So we did not tell the investigators or the patients what brand or type of aspirin to use. It was left as at the discretion of the physician and patient. I don't know that we collected whether it was enteric coated or not.

DR. PRESSLER: Milton Pressler, Pfizer again. We did not. Presumably, many of the patients took enteric-coated aspirin as well as immediate-release aspirin. We did not collect that. We did specify that the dose be less than or equal to 325 milligrams a day.

DR. NISSEN: We also did instruct people. We recommended that they take it 2 hours before their NSAID. But we have no way to verify whether

they actually did or did not do that and so there's just only so much information.

Again, since we weren't randomizing to aspirin, this was not something we could easily control. And we couldn't randomize to aspirin, particularly for the secondary prevention population.

DR. NEILL: Did you have a follow-up?

DR. HO: Yes. I just wanted to ask about , over time, was use of aspirin assessed in subsequent study visits? And how was that done?

DR. NISSEN: Yes. I'm going to ask Kathy Wolski, who has actually looked at that, to talk about it.

DR. WOLSKI: Kathy Wolski, biostatistician, Cleveland Clinic. Could you repeat the question? I'm sorry.

DR. HO: Yes. So was aspirin use assessed in subsequent study visits other than baseline?

DR. WOLSKI: Yes, it was asked at every visit, so we do have information that was collected, start and stop times for aspirin

throughout the study. And most people who started on aspirin stayed on aspirin.

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: Rosenberg. A couple of follow-up questions; some of the additional slides you presented first on the cross-in or cross-overs -- do you have more information on which drugs a patient is cross-in or crossover to and on multiple use of drugs after this?

Also, it's a good question, the causes of discontinuation of the trial. There's a lot of others. I know there was some additional analysis presented, but some of this discontinuation to crossover also to therapy.

DR. PRESSLER: Milton Pressler, Pfizer. We have the information on what patients crossed in and over to. The most detail we have is particularly on aspirin. We were tracking whether patients adhered to aspirin or not.

The trial had some pre-specified rescue treatments, which we had enumerated. Dr. Nissen enumerated them in his description and a lot of

those were opioids. So we can perhaps a little later provide you a more detailed breakdown on that.

DR. ROSENBERG: Yes. I was more interested in, for example, a number of patients on coxibs who started ibuprofen, and here is the drug, and vice versa.

DR. NISSEN: Yes. Let's put that up here. So this is slide SA-185. Can you project that? So here is the data. And these are at least 1 day of treatments. You can see non-randomized. This is percent celecoxib, non-randomized, ibuprofen, non-randomized, naproxen, and then all other NSAIDs, so this is the different types of cross-ins.

DR. PRESSLER: That said, most of the time when people needed pain relief, they were treated with an opioid.

DR. NEILL: Dr. Cunningham?

DR. CUNNINGHAM: Thank you. Melody Cunningham. So my question is a follow-up to that. So you said that most were treated with opioid. I was wondering in this day and age did the doses

look different in the different categories of treated patients in terms of how much opioid and how frequent, and did you gather that information.

DR. PRESSLER: In this case, maybe the perspective of one of our investigators would be helpful. Stan, you were treating these patients. What did you do when somebody wasn't responding or had a flare?

DR. COHEN: Stanley Cohen, Dallas. So I mean, the reality was that, if patients had pain and were not doing well on this study, we would generally remove them from the study. It was great coaxing by the steering committee to keep people in the study as long as we could. We did what we could.

Some were more comfortable with opiates, some physicians; some were not. So I can't really comment on the dose and that type of thing. Clearly, we used as minimal dose as we could get away with. And we could do some injections, things of that nature if we had to.

But primarily, if they had pain and it was

not being banished, they left the study. So I don't know if that addresses your question, but certainly, I can tell you our experience was the least dose we could use of rescue medicine to control it.

DR. CUNNINGHAM: I actually had a comment and one other question. So when you looked at the safety with these medications with aspirin, I kept hearing that there was no evidence of interaction, but I guess I would actually say there was no evidence of negative interaction. Right, because when it was associated with when it was looked at with the aspirin it was better?

DR. NISSEN: Point well taken.

DR. CUNNINGHAM: The other probably is for Dr. Cohen, but maybe for each of you. And it's just thinking of the GI side effects and, most often, we worry about bleeding, but we also know that these are inflammatory states and all of these patients probably have elevated hepcidin and then have, you know, lack of iron absorption because of that.

Was that looked at in terms of the degree of anemia or whether it was actual bleeding or whether it was anemia of chronic inflammation?

DR. NISSEN: These were all adjudicated, but there's a lot of uncertainty. I mean, obviously the anemias didn't all get worked up. It wasn't part of the study plan to do that. Individual physicians would make their own mind up about how to pursue it.

But the central adjudicators were asked to try to determine whether the fall in hemoglobin or hematocrit -- where there was evidence that it was of GI origin. And then that was part of the adjudication process.

So actually, if we could show the slide ST-47, this just shows you the standards that were used. So you can see we had clinically significant iron deficiency defined as GI origin, excluding esophagus causes other than it rose to esophagitis. Then you can read for yourself what the actual definitions that were used were.

They had to not have -- no non-GI source

could be identified and so on. So this adjudication process was as rigorous as we could make it, given the uncertainties about anemia that exist in a population that develops anemia.

DR. NEILL: Dr. Richards?

DR. RICHARDS: Steuart Richards, V.A. Pittsburgh, adult rheumatologist. Do you have any data on adherence or compliance with the study medications? And did that decrease over the course of the study?

DR. PRESSLER: Milton Pressler, Pfizer. Maybe I need to have a little more clarification. We were tracking the patients at their follow-up visits. We didn't use MEMS or anything of that nature, given the scale of the study and so forth, if that is helpful, but we were tracking whether patients brought back their pills or not, similar to other clinical trials.

DR. RICHARDS: So that was a question. Did you do pill counts with the returned medications to get an estimate of the adherence?

DR. PRESSLER: Yes, yes. We did not have

any additional means of fidelity, though, such as if you're referring to some of the embedded chips in the caps, the so-called MEMS devices, we didn't use that.

DR. RICHARDS: Correct, but I just wondered if you had data on how adherent the patients were. I didn't hear that data presented.

DR. PRESSLER: I don't know the answer off hand to give you more precise information there.

DR. NEILL: Dr. Ohman?

DR. OHMAN: Yes, Magnus Ohman. First of all, I want to congratulate the PRECISION investigator for a heroic effort. The trial went much longer than projected and yet was concluded.

But I have a specific question regarding the number of events. It was originally set out to be a non-inferiority safety trial with 762 events. It was retooled to a lower event rate, now with much larger confidence intervals.

So based on the original calculation, it looks like the trial may have been 30 percent underpowered. And what impact does that have if

one is to ascertain safety in a non-inferiority trial?

DR. NISSEN: Yes. So just what we did here is we originally planned, as you point out -- you're absolutely right -- to have 762 events. We were monitoring event rates. Interestingly enough, all members of the executive committee were blinded to the event rate except for me.

I was the only one that was allowed to see this. And in discussions with Tom Fleming, who chaired our data monitoring committee, it was very clear that the event rates in this population were actually a lot lower than we had anticipated. One of the reasons the trial took so long was that these patients actually did pretty well.

As we've seen now recently in cardiovascular trials, we've seen a lowering of event rate. And so the alteration was made based upon achieving 80 percent power rather than 90 percent power. And that shrank the number of required events down to 580.

So in other words, we accepted lower power

to achieve the confidence intervals that we originally had specified. That was obviously a risk to the sponsor, but we thought it was reasonable. We did discuss this with FDA.

Everybody; the agency, ourselves, the medical community; wanted an answer and we were willing to accept a little bit less power in order to try to get the trial actually done.

We actually considered midway through the trial in dropping the ibuprofen arm and just comparing to naproxen because there was this sense that maybe naproxen was cardioprotective. And FDA counseled us and they said, "Don't do that," and in retrospect, I think they were right because we did see in fact some differences.

I think having three rather than two NSAIDs turned out, but that makes for a much longer and much bigger trial, but I think it did give us some useful information.

DR. NEILL: Thank you very much. I have five members still waiting to ask questions. Dr. Tchetgen Tchetgen, whose name I am confident I

am mispronouncing, Dr. Schmid, Meisel, Hendrix, and Parker.

Some of you have been meetings with me before, but now is a good time for me to point out that I have an obsessive attention to staying on time and it's time for lunch. So I want you to make a note of the questions that you have and I will point out that there will be time for additional clarifying questions at two different opportunities this afternoon and then throughout the day tomorrow.

I don't want to minimize in any way the importance of your question or the discussion that they may prompt, nor the importance of lunch. So we will now break for lunch. We will reconvene again in this room in one hour, at 1:40 p.m. Please take any personal belongings you may want with you at this time.

Committee members, please 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. I will see

you at 1:40.

(Whereupon, at 12:40 p.m., a lunch recess was taken.)

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

(1:40 p.m.)

DR. NEILL: Good afternoon. It's now 1:40. I'd like to call us back to order. And without further ado, we'll now proceed with more FDA presentations.

FDA Presentation – Anjelina Pokrovnichka

DR. POKROVNICHKA: Good afternoon. My name is Anjelina Pokrovnichka and I'm a medical reviewer in the Division of Anesthesia, Analgesic, and Addiction Products. My presentation today will outline features of the trial design that are important to keep in mind when interpreting the results from PRECISION.

However, my goal is not to repeat the details of the trial design, as they have been presented already by Pfizer. I will cover some of the trial results and then Dr. Bo Li from the Office of Biostatistics will present the findings from the primary endpoint analysis.

I will continue with general safety findings from PRECISION followed by summary findings from

the ambulatory blood pressure monitoring substudy. Finally, I will summarize the findings of the epidemiology literature review covering the four-year period since the last epidemiology review of this safety issue.

Before I get into the trial design, I would like to point out that the trial was not intended nor designed to compare efficacy. There are several reasons why this is the case. The trial did not require a particular baseline pain score as eligibility criterion, washout of prior non-steroidals, and non-non-steroidal pain medications was not required.

Therefore, the baseline pain score could have been collected while patient was on those medications. If baseline pain score was not assessed properly, any change from baseline is uninterpretable.

Patient population included subjects with clinical diagnosis of osteoarthritis or rheumatoid arthritis receiving chronic analgesia, any type of chronic analgesia, for at least 6 months who, in

the investigator's opinion required and were eligible for chronic daily therapy with non-steroidals, regardless of the dose of any non-steroidal that was used prior to enrollment.

Subjects enrolled in PRECISION had established cardiovascular risk or at risk for cardiovascular disease as defined in details in the FDA briefing document. Rheumatoid arthritis patients requiring disease-modifying therapy should be on a stable regimen.

It is important to know that the highest-risk patients most dependent on the platelet-inactivating effect of aspirin, for example those who had recently experienced a cardiovascular event such as myocardial infarction, stroke, or CABG surgery within 3 months prior to randomization were not eligible for enrollment.

Subjects with history of ulcer within 2 months or GI bleed within 6 months were excluded. Subjects with creatinine above pre-defined levels were also excluded.

This is the one I was looking for. At

randomization, all subjects received the lowest dose allowed in the trial for the assigned treatment. Titration up or down was allowed at all subsequent study visits.

However, dosing for celecoxib in osteoarthritis was generally limited to 100 milligrams twice a day per approved labeling. As described in the labeling, there is a dose response for cardiotoxicity and the previously highest dose approved, 400 milligram twice daily, for another indication has been removed from the labeling.

As we know, the safety of the non-steroidals is dose-related. The safety outcomes must be interpreted in the context of the doses that patients actually received in each treatment group.

Non-steroidals that were non-study medications and aspirin over 325 milligrams were prohibited for use during the trial. However, the protocol allowed for aspirin cardioprophylaxis and other medications to optimize the treatment of their cardiovascular disease.

Subjects already taking low-dose aspirin

were allowed to continue regardless of their cardiovascular risk profile. During the trial, subjects with a high relative cardiovascular risk were evaluated for the need of anti-platelet therapy and low-dose aspirin was introduced at the discretion of the investigator.

Subjects were instructed to take aspirin 2 hours before study drug to minimize the potential for an interaction with the study drugs that may reduce the anti-platelet effects of aspirin. And as mentioned previously, all subjects received a gastroprotective agent.

The protocol, pre-defined, non-non-steroidal rescue medications for patients on treatment and for those who discontinued treatment but stayed in the trial. Because one of the components of the primary analysis evaluated events within 30 days of study drug discontinuation, it was required that subjects who prematurely discontinued study drug treatment not be treated with open-label celecoxib, naproxen, or ibuprofen for the 30 days following discontinuation of study drug.

In addition, it was strongly recommended, but not required that subjects not be treated with any open-label non-steroidal, but be managed with a designated analgesic rescue therapy during the follow-up through completion of the trial.

Patients who discontinued treatment were encouraged to remain in the trial for continued follow-up with the reasons for both discontinuing treatment and trial being captured; specifically, patients who experienced any events related to the endpoints of the trial who were to be discontinued from treatment and followed.

I'm sorry. It seems like I'm pointing to the screen. This is the TV and I actually have to point to the screen in front of me. So the sponsor has already covered many of the results of the PRECISION trial. As summarized on this slide, the FDA presentation of the results from PRECISION will focus on further characterizing the trial population to put the trial results into context for the committee.

Our review of the primary analysis,

additional analysis we undertook to evaluate for clinical evidence of an aspirin drug-drug interaction and our assessment of the secondary and tertiary endpoints followed by a discussion of general safety.

The ITT population included all randomized subjects. The modified ITT population included all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline visit and the safety population included all patients who received at least 1 dose of study drug.

The analysis performed on the ITT and the modified ITT populations differed, which will be described by Dr. Li, who will provide the statistical presentation.

The majority of the trial population was comprised of white female subjects with osteoarthritis, there were no major differences between treatment groups in the baseline characteristics. The use of disease-modifying anti-rheumatic drugs, DMARDs, in patients with rheumatoid arthritis was comparable between

treatment groups.

Most of the subjects had no evidence of active cardiovascular disease, but the trial population was enriched for those at risk for cardiovascular disease. 46 percent used aspirin at baseline and additional 4 percent were prescribed aspirin prior to starting study drug.

An important note is that, because subjects enrolled were primarily osteoarthritis patients, the dose of celecoxib was capped at 200 milligrams per day. The low number of patients with rheumatoid arthritis precludes a robust evaluation of the safety for the 400-milligram-a-day dose.

Patients on naproxen and ibuprofen had no similar restrictions of the dose for osteoarthritis and the doses administered were the prescription doses, while some patients may be adequately managed on the over-the-counter doses.

The top row of the table shows the duration of follow-up across treatment groups for the ITT population. The bottom table show the duration of treatment across groups for the safety population.

The median values for these parameters were similar across groups except that the median treatment exposure for the ibuprofen group was slightly shorter than the other two groups. 113 patients out of the 307 who experienced an APTC event stayed on study drug treatment for at least some duration following the event despite the protocol-specified requirement for discontinuation of the study drug at the time of an APTC event.

As illustrated in the table, about 20 percent of patients with an APTC event continued taking study drug for longer than 1 month after the APTC event occurred. Out of the 113 subjects who continued to take study drug after their first APTC event, 4 subjects experienced a second APTC event while on treatment.

Another 2 subjects experienced a second APTC event after treatment discontinuation, but within 30 days of treatment discontinuation.

The table on this slide illustrates the mean individual dose administered in this trial for each treatment for all subjects and for subjects with

osteoarthritis and rheumatoid arthritis. As I mentioned, due to the fact that 90 percent of the patient population were patients with osteoarthritis for whom the celecoxib dose was limited to 100 milligrams twice a day per labeling, most patients randomized to celecoxib received that dose.

Therefore, when interpreting the results, the lower dosing regimen of celecoxib is being compared to relatively higher doses of ibuprofen and naproxen. Consistent with the mean individual doses observed for each treatment group and a dosing guidance in labeling, very few patients in the celecoxib group with osteoarthritis dose escalated.

In contrast, half of the patients in the celecoxib group with rheumatoid arthritis and half of all the patients in the ibuprofen and naproxen groups dose escalated. Approximately 60 percent of the patients who dose escalated and comparable between treatments remained on the escalated dose for over 1 year.

Seventeen percent of all subjects were reported to have used concomitant celecoxib, naproxen, or ibuprofen, a finding that was similar between the three treatment groups. Concomitant use of any non-steroidal that were not study medications was reported for 28 percent of subjects in the ITT population. This finding was also similar across the three treatment groups.

The proportion of subjects who used rescue medications for pain was similar across treatments; specifically the pattern of rescue medication used, type of rescue, and number of users was similar across the three treatment groups.

The most commonly used rescue medications were from the opioid drug class. 24,081 subjects were randomized in PRECISION and 23,953 were treated and had at least 1 post-baseline visit. Subjects who were treated could have completed treatment or discontinued treatment.

Subjects who discontinued treatment were encouraged to remain in the trial, to continue follow-up, but could discontinue from the trial.

Even though 68 percent of the treated subjects discontinued study drug, 70 percent were followed after treatment discontinuation and completed the study.

Reasons for discontinuation at the time of treatment discontinuation and/or the time of study discontinuation were captured. However, the end of study case report form page did not allow adverse events or insufficient clinical response to be the reason for study discontinuation even if that was the underlying reason for discontinuing.

We ask sponsors to avoid reporting the reason for discontinuation as some variation of subjects not wanting to participate if it can be determined that the actual reason was lack of efficacy or adverse events.

Initially, a large proportion of subjects were reported to discontinued treatment due to the reasons no longer willing to participate in the study, other, and withdrew consent. We asked the applicant to evaluate the subjects who discontinued either treatment or trial due to these reasons to

see if any of these miscellaneous reasons were actually representing adverse events or lack of efficacy.

The results I'm going to show you for treatment discontinuation and study discontinuation on this slide and the next slide are the results of this reclassification process. The leading reason for treatment discontinuation, relatively balanced between treatment groups, was an adverse event followed by no longer willing to participate, insufficient clinical response, and other.

The leading reasons for trial discontinuation balanced between treatment groups were loss to follow-up, no longer willing to participate, and withdrew consent.

The statistical analysis plan and the results of the Division's analysis of the primary endpoint will now be presented by Dr. Li.

FDA Presentation – Bo Li

DR. LI: Good afternoon. My name is Bo Li. I'm a statistical reviewer from the Office of Biostatistics. Today, I will present our findings

from a statistical assessment of cardiovascular safety of celecoxib based on the PRECISION trial.

I will first give a brief overview about the PRECISION trial, including its trial design and the statistical methods. I will only repeat the key stuff as you've already heard a few times. Then I will talk about the analysis results of the cardiovascular outcomes in PRECISION followed by the summary of our statistical assessment.

An overview of the PRECISION trial; PRECISION is a multi-center, randomized, double blind, triple-dummy, active-controlled, 3-arm parallel group, event-driven cardiovascular outcome trial. PRECISION enrolled osteoarthritis and rheumatoid arthritis patients with established cardiovascular disease, or with risk factors for cardiovascular disease.

Subjects were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups, celecoxib, 100 to 200 milligrams twice daily, ibuprofen, 600 to 800 milligrams three times daily, and naproxen, 375 to 500 milligrams twice daily.

The primary safety outcome of PRECISION is the APTC composite endpoint, comprised of three components; cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. APTC events were adjudicated by a clinical events committee based on pre-specified diagnostic criteria and operational procedures.

This trial used a non-inferiority design with the objective to rule out pre-specified excess risk of the APTC events for celecoxib compared to both naproxen and ibuprofen. Two analysis populations were used. The ITT population included all randomized subjects. The modified ITT population, mITT, included all randomized subjects who took at least 1 dose of study drug and had at least 1 post-baseline study visit.

The primary analysis employed two censoring schemes to capture the primary CV events. Per the study protocol, subjects who discontinued the study drug prematurely were to be followed through the end of the study. In the ITT analysis, APTC events were ascertained using an on-study censoring scheme

which included events that occurred during both the active treatment period and any follow-up period after treatment discontinuation.

The mITT analysis used an on-treatment censoring scheme to capture an APTC event that occurred while subjects were exposed to randomized treatment, or within 30 days after the end of treatment.

The PRECISION trial was originally designed to demonstrate non-excessive CV risk of celecoxib versus naproxen and ibuprofen based on the following criteria. The point estimate of hazard ratio did not exceed 1.12 for both ITT and mITT analysis.

The upper bound of the two-sided 95 percent confidence interval of the hazard ratio estimate was below 1.33 for both ITT and mITT analysis. A total of 762 APTC events were needed in both analyses to achieve 90 percent power to rule out the 1.33 risk margin.

According to the original study protocol, the study would continue until 762 APTC events had

occurred in the mITT analysis and all subjects had the opportunity for at least 18 months of follow-up. Subjects were intended to receive study treatment and to participate in study visits through the event-driven completion of the study.

No maximum length of study participation was specified in the original design.

After the trial started, a lower-than-expected event rate and higher-than-expected treatment discontinuation rate were observed. Due to the slow accrual of the primary CV event, Pfizer approached the agency to discuss possible changes to the study design as recommended by the data monitoring committee.

Some of them were accepted by the agency and were reflected in two major protocol amendments while the trial was ongoing. The amendment dated on May 6th of 2010 documented a power reduction from 90 percent to 80 percent. To achieve 80 percent power, the total number of events needed is 580 for both ITT and mITT analysis.

This amendment also specified a maximum

length of study participation of 42 months. Another major amendment was dated on July 7th of 2011. Due to the high treatment discontinuation, the risk margin for mITT analysis was changed to 1.4. Accordingly, the total number of APTC needed for the mITT analysis was further reduced to 420.

This amendment also specified that the ITT analysis would truncate data by month 30 to limit the potential impact of early treatment discontinuation on the ITT analysis. And mITT analysis would truncate data by the maximum treatment duration of 42 months plus a 30-day off-treatment observation window.

The pre-specified primary analysis was a time-to-event analysis of first adjudicated APTC event based on an on-study by 30 months [indiscernible] ITT analysis and, on treatment plus 30 days, mITT analysis as I just discussed.

A Cox proportional hazards model was used to calculate the hazard ratio and its 95 percent confidence interval. The Cox model included treatment as the explanatory variable and also

included other covariates for type of arthritis, baseline use of low-dose aspirin, and geographic region.

A few CV-related outcomes were pre-specified as secondary or tertiary endpoints and subject to adjudication. Among them, I will discuss the secondary endpoint MACE, which is a 6-component composite including the 3 components of APTC plus revascularization, hospitalization for unstable angina, and hospitalization for transient ischemic attack.

MACE was referred to as expanded MACE by Dr. Nissen. Death from any cause was another element that was evaluated as part of the CV risk assessment. MACE and all-cause deaths were analyzed using the same time-to-event method for the primary APTC event.

There were other adjudicated GI and renal endpoints. In my presentation, we will focus on the assessment of CV safety so we will not discuss these endpoints.

However, it is important to note that,

except for the primary APTC, all other endpoints, including GI and renal endpoints, though pre-specified and adjudicated, were not part of a pre-specified hierarchical testing plan. Therefore, their analysis results either for the overall study population or for the subgroups by aspirin use should be interpreted as exploratory.

Now, I move on to the analysis results of the PRECISION trial. Sorry for that. The randomization started in October of 2006 and ended in June of 2014. The last subject last visit occurred on April 12th of 2016. A total of 24,081 subjects were randomized at 923 study centers globally, including 8,072 subjects randomized to receive celecoxib, 8,040 subjects randomized to receive ibuprofen, and 7,969 subjects randomized to receive naproxen.

This comprised the ITT population I've highlighted in the blue box. A total of 16,865 subjects completed the study follow-up until 42 months or the study termination in 2016. That comprised 70 percent of the ITT population. 7,031

subjects did not complete their study follow-up, which corresponds to an early study discontinuation rate of 29 percent.

The study drop-out rate appears similar across the three treatment arms. A total of 23,955 subjects took at least 1 dose of study drug. 7,511 subjects completed study treatment. That represents 31 percent of all randomized subjects.

While majority of randomized subjects discontinued treatment prematurely, the overall early treatment discontinuation rate is approximately 68 percent. The treatment discontinuation rates appear similar in general across the three arms, with a slightly higher percentage observed in the ibuprofen group than the other two groups.

Two treated subjects did not contribute any post-baseline study visit. Thus, the mITT population included a total of 23,953 subjects. This slide shows a Kaplan-Meier plot of time to early study discontinuation. Study dropout was gradual and the dropout rates were similar across

the three arms over time.

Approximately 20 percent of ITT subjects withdrew from the study prematurely within 30 months since randomization. This plot shows the distribution of the time to premature treatment discontinuation by treatment group. The Kaplan-Meier curves are generally close to each other. The ibuprofen group showed a slightly higher treatment discontinuation than the other two groups throughout the study duration.

The curving down shape of the curves reflected a higher discontinuation at the early stage of treatment. This slide summarized observation time for the two primary censoring schemes. For the ITT analysis using the on-study censoring through 30 months, the mean follow-up duration is over 2 years, similar for all three arms.

Each arm has a total follow-up duration ranging from 17,058 person-years to 17,281 person-years. In the on-treatment mITT analysis, mean observation time is around 20 to 21 months for each

arm, which is shorter than that of the ITT analysis due to the high treatment discontinuation.

The total observation time for the on-treatment analysis ranges from 13,306 person-years for ibuprofen group to 14,203 person-years for celecoxib group.

The primary analysis results of APTC event; in ITT analysis, a total of 607 subjects experienced a positively adjudicated APTC event, including 188 in celecoxib arm, 218 in ibuprofen arm, and 201 in the naproxen arm.

The corresponding percentage and incidence rate are shown for each arm. The incidence rates are 1.1, 1.3, and 1.2 per 100 person-years for celecoxib, ibuprofen, and naproxen respectively. Employing the pre-specified Cox regression model, the hazard ratio estimates and its 95 percent confidence interval were obtained and shown here for the two pairwise comparisons, celecoxib versus ibuprofen and celecoxib versus naproxen.

Note that our focus is the relative safety of celecoxib compared to the two non-selective

NSAIDs. As such, I will only present the pairwise comparisons involving celecoxib and leave out the one of ibuprofen versus naproxen for the rest of my presentation.

One-hundred and thirty-four, 155, and 144 first APTC events were captured on treatment plus 30 days for celecoxib, ibuprofen, and naproxen group respectively. The total number of events observed on treatment is 433. Incidence rates were slightly lower than those observed in the ITT analysis.

These are the hazard ratio estimates and the 95 percent confidence intervals for the mITT analysis using the same Cox model. For both pairwise comparisons, the 95 percent confidence interval contains the null value of 1 for both ITT and mITT analysis.

The hazard ratio point estimates are all below 1.12. In the ITT analysis, the upper limit of 95 percent confidence interval is lower than the pre-set risk margin of 1.33 for both celecoxib versus ibuprofen and celecoxib versus naproxen.

In the mITT analysis, the upper bound is lower than the pre-set risk margin of 1.4 for both pairwise comparisons. Therefore, the primary analysis results met all pre-specified criteria of non-excessive CV risk for celecoxib relative to the two non-selective NSAID comparators.

This is a Kaplan-Meier plot of APTC events comparing the three arms using the on-study censoring. The X axis is time to event in months, up to 30 months. The Y axis is estimated percentage of APTC events, with a scale ranging from 0 percent to 4 percent.

The Kaplan-Meier curves showed how the events accumulated over time. The curves for celecoxib and naproxen were generally close to each other as the ibuprofen group arm showed a numerically slightly higher proportion of subjects who experienced a primary APTC event.

These curves in the plot resemble straight lines and suggest that the APTC event rate was approximately constant over time within each treatment arm. This is a Kaplan-Meier plot for the

mITT on-treatment analysis. The X axis is now up to 42 months. Similar to the ITT plot, the event rate appears approximately constant over time within each group.

In the primary ITT analysis, early study withdrawal rate was about 20 percent by month 30. Pfizer conducted this sensitivity analysis to assess the impact of potential informative censoring among these early withdrawal subjects. Seven classes of adverse events were identified based on their potential association with myocardial or vascular events.

The observed incidence rate of APTC among subjects with and without these adverse events were calculated and then used to impute the additional APTC among early withdrawal subjects based on presence or absence of any of those AEs and expected missing follow-up time of these subjects.

These imputed APTC events were finally combined with observed events in the ITT analysis. A logistic regression model was used to calculate the odds ratio and its associated 95 percent

confidence interval to evaluate the impact on the primary ITT analysis results.

I'll quickly go over the results of Pfizer's sensitivity analysis, since Dr. Nissen already presented. I'll go over this with a little bit more detail about them. Approximately 1,300 subjects in each arm withdrew study early without experiencing an APTC event.

A breakdown depending on whether the subject experienced any of the selected AEs are shown here. The number distributed evenly across arms as well as the subjects' total expected missing follow-up time.

As a result, similar numbers of additional APTC events were imputed. That is 20 on celecoxib, 22 on ibuprofen, and 20 on naproxen. When combining with observed events, the odds ratio estimates are almost identical as estimates based on observed events only, including their upper bounds.

Thus, this analysis does not alter the primary analysis, ITT analysis results.

Informative censoring would impact the study results when they are imbalanced across arms. Based on Pfizer's analysis, no differential informative censoring was identified between celecoxib and the other two arms.

We further calculated the number of imputed APTC events needed on celecoxib to tip the results while fixing the number of imputed APTC as 22 for ibuprofen and 20 for naproxen.

So this slide shows that, when compared to naproxen, in order for the upper bound of the 95 percent confidence interval to reach 1.33, a total of 247 APTC events were needed for celecoxib, which means 59 additional events were needed. Compared to the 20 imputed events, this implies that the event rate in the early withdrawal subjects of the celecoxib group needed to be about 3 times higher than the other two groups.

Similarly, for celecoxib compared to ibuprofen, 80 additional events were needed to tip the results. That is a 4 times higher event rate for celecoxib arm relative to the other two arms.

This scenario appears unlikely given that the reported adverse events, the rate and the reason of study withdrawal, and the characteristics of early withdrawal subjects were similar among the three treatment arms of PRECISION.

The time to first occurrence of APTC event was evaluated for specific subgroups defined by baseline of aspirin, baseline demographic characteristics, including age, gender, race, and region, and baseline disease factors, including primary diagnosis of RA or OA, established cardiovascular disease, diabetes, and smoking status, using both the ITT and mITT analysis.

All baseline subgroup analyses show consistent results among subgroups. The ITT analysis results of all baseline subgroups were included in the background document. Exploratory analyses were attempted to assess the effect of dose escalation on the incidence of APTC events.

However, the interpretation of this post-randomization analysis was limited by the fact that PRECISION was not designed nor powered to assess

the dose dependency of APTC events. Subjects could switch between high and low doses throughout the study.

Therefore, it's difficult to attribute causality of APTC events to any given dose. For these reasons, we will not discuss analysis of CV risk by dose any further.

Among the baseline subgroups, the one by baseline use of low-dose aspirin for cardioprotective purposes was of special interest. The next two slides will focus on this subgroup analysis. As you already heard, approximately 46 percent of all randomized subjects took low-dose aspirin for cardioprotection at the study entrance. The forest plots in this slide depict the subgroup analysis results for celecoxib compared to naproxen with the ITT analysis shown on the top and mITT analysis shown at the bottom.

The estimated hazard ratios of APTC are consistent for subgroups with or without baseline usage of aspirin. There's no significant treatment by subgroup interaction observed in both analyses.

All confidence intervals covers a null value of 1.

For celecoxib compared to ibuprofen, consistent results were obtained for subgroups with or without baseline usage of aspirin in both ITT and mITT analysis. Note that all analyses presented from this slide are considered exploratory.

The top part of this table repeated the primary ITT analysis of APTC. The counts of subjects experienced each individual APTC component event and its time-to-event analysis results were shown at the bottom. The hazard ratio for CV death, non-fatal MI, and non-fatal stroke was calculated separately using a similar Cox regression model as that used in the primary analysis.

In this table, some subjects experienced more than one type of event and each type of event was analyzed independently. Therefore, the sum of the component events is larger than the total number of subjects who experienced APTC. The analysis results appear consistent across the three

types of CV event.

The 95 percent confidence interval for each of the three events includes a null value of 1 for the two pairwise comparisons. Here, I show the analysis results for the secondary endpoint MACE, the 6-component composite. Due to the broader definition, the number of subjects who experienced a MACE is higher than the number of subjects who experienced APTC.

The hazard ratio estimates of MACE were consistent with the estimates of the primary APTC endpoint for the ITT and mITT analysis. A total of 621 deaths were adjudicated during the PRECISION trial. This table depicts the time-to-event analysis results for all-cause deaths based on both ITT and mITT analysis.

A total of 437 deaths occurred during the study by month 30, with 132 occurring in the celecoxib group, 142 in ibuprofen, and the number of deaths in the naproxen group is 163, the highest numerically. The mITT analysis included a smaller number of deaths captured on treatment and the same

numerical order were observed.

No additional concern for the relative safety of celecoxib was raised from the time-to-event evaluation of adjudicated deaths. You will hear more details for examination of deaths in the PRECISION trial in Dr. Pokrovnichka's presentation.

Now, I will share the high-level summary of our statistical assessment of CV safety of celecoxib based on PRECISION.

PRECISION is a large-scale safety study designed to rule out excess cardiovascular risk for celecoxib versus naproxen and ibuprofen. The trial randomized more than 24,000 subjects. The mean treatment exposure is 20 months. A high early treatment discontinuation rate was observed, which is 68 percent.

The average follow-up time during study is 34 months. 29 percent of all randomized subjects prematurely withdrew from the trial. The pre-specified primary analysis results of APTC endpoint showed no evidence of excess CV risk associated with celecoxib compared with naproxen and ibuprofen

at the doses studied.

This finding was supported by various sensitivity analyses we conducted and analysis of other CV-related endpoints. This concludes my presentation. Thank you for your attention. I will now give the podium back to Dr. Pokrovnichka.

DR. POKROVNICHKA: I've learned that this is not a remote control for the TV, so I'll be on the right slide. Because of the concerns of an aspirin drug-drug interaction with celecoxib, ibuprofen, and naproxen, we evaluated APTC events based on aspirin use.

Dr. Li discussed the subgroup analyses on the APTC endpoint by baseline aspirin use. In the next couple of slides, I will present additional analyses of APTC events. This table shows the number, the percentages, and incidence rate of subjects who were on aspirin and experienced an APTC event compared to those subjects who were not on aspirin.

Across all three treatment groups, the incidence rates of APTC events were higher in

patients receiving low-dose aspirin compared to non-aspirin users, likely driven by the fact that aspirin users are at higher baseline risk for cardiovascular events.

There were no differences in the incidence rates of APTC events for low-dose aspirin users across treatment groups. This is not surprising because, even though ibuprofen and naproxen can block the effect of low-dose aspirin, they themselves inhibit COX-1 at prescription doses.

Additional cardiovascular, GI, and renal safety and all-cause mortality outcomes based on adjudicated events were assessed as secondary or tertiary endpoints in PRECISION and this analyses have been presented by Pfizer.

The applicant conducted statistical testing and reported nominal confidence intervals and p values for these outcomes, despite the lack of a pre-specified hierarchical statistical testing plan.

Therefore, the analysis results for these endpoints should be considered exploratory or

hypothesis generating only and interpreted descriptively rather than relying on the nominal p values.

This table summarizes the secondary and tertiary analyses of adjudicated events by treatment group. The definitions for clinically significant GI and renal events were provided in the FDA briefing document.

The numbers of events for all of these outcomes were very low overall and the differences between treatment groups were very small. Major adverse cardiovascular events, the so-called MACE, were presented by Dr. Li in her talk.

Now, we'll move on to the general safety and the following slides will describe the data observed in PRECISION. And to repeat a theme, these data should be interpreted in the context of the permitted dosing ranges for celecoxib and for ibuprofen and naproxen, particularly when many of the non-steroidal-related adverse events are known to be dose dependent.

Deaths were recorded on the case report form

as an end-of-study status, but 14 were only captured on the adverse event page of the case report form. And that is why there are different results. Regardless, the proportion of subjects who died for both datasets, CRF and adjudicated dataset, was similar between the three treatment groups.

The incidence of deaths during the 30 days following study drug discontinuation was higher for all 3 treatment groups as compared to the incidence of death on study drug and the incidence of death beyond the initial 30-day follow-up period.

This pattern persisted for cardiovascular death as a separate outcome. Investigators were instructed to record the reason for study drug discontinuation as death for those cases where the death occurred a few days after the subject stopped the study drug.

As you can see, that accounted for most of the reasons for study drug discontinuation among those who died during the 30-day post-study drug period. However, further investigation

demonstrated that an adverse event in the 7 days preceding study drug discontinuation was recorded for a third to half of these cases.

More deaths occurred in the RA population, 3.7 percent compared to the OA population, 2.5 percent. Among the osteoarthritis population, the proportion of subjects who died from all causes was similar between treatment groups.

However, the proportion of rheumatoid arthritis patients who died from all causes was highest in the naproxen group, followed by the ibuprofen and then the celecoxib group. These results were found for both the cardiovascular and non-cardiovascular events.

This analysis was limited by being a post-randomization analysis with very few subjects. It is interesting to noted that a higher proportion of subjects in the naproxen group who died were using disease-modifying anti-rheumatic drugs and the leading cause of non-cardiovascular deaths were infections and malignancies.

However, DMARD use at baseline and during

the study was balanced across the three treatment groups. The proportion of subjects who experienced a treatment-emergent serious adverse event was similar between the three treatment groups. The most frequently reported serious adverse event by system organ class term were within the cardiac and gastrointestinal disorders.

This table shows selected serious adverse events typical of the NSAID class. Overall, the incidence of these serious adverse events was lower for the celecoxib group compared to the ibuprofen and naproxen groups, but the differences were very small.

Treatment-emergent adverse events that were observed in more than 1 percent of subjects in any treatment group leading to treatment discontinuation were comparable between the three groups, except for hypertension and blood creatinine increase, for which fewer patients from the celecoxib group discontinued treatment compared to ibuprofen and naproxen.

The proportion of subjects who experienced a

treatment-emergent adverse event was similar between the three treatment groups with approximately 82 percent of subjects having onset of these adverse events between 0 and 6 months.

The most frequently reported adverse events by preferred term are listed in the table on this slide. The proportion of subjects with these events was lower in the celecoxib group compared with the ibuprofen and naproxen groups.

A 4-month ambulatory blood pressure monitoring so-called ABPM substudy, was included in PRECISION. The primary endpoint was the change from baseline and 24-hour average systolic blood pressure at month 4. Analysis of covariants however was performed to model the effect of treatment on the change in 24-hour systolic blood pressure with baseline 24-hour systolic blood pressure.

The study was powered to detect at least 3 millimeters mercury difference among treatments. The study found that, after 4 months of therapy, treatment with celecoxib was associated with an

average of 3.9 millimeters mercury lower 24-hour systolic blood pressure compared to ibuprofen.

This observed difference was primarily driven by a mean elevation of systolic blood pressure by 4 millimeters' mercury with ibuprofen while there were minimal changes with celecoxib.

Exploratory analysis showed that the difference appeared greater in females compared to males, 6.3 millimeter mercury for female and 1.4 millimeters' mercury for males. A mean elevation of systolic blood pressure by less than 2 millimeters' mercury with naproxen was also observed, but the difference between celecoxib and naproxen did not reach statistical significance.

The Division of Epidemiology reviewed the epidemiology studies on NSAIDs-associated thrombotic cardiovascular risk in 2013. The findings of the review were discussed in 2014 at a joint advisory committee meeting. As Dr. Racoosin mentioned earlier, while these epidemiology studies provided some insights into the non-steroidal anti-inflammatory drug-associated cardiovascular risk,

they did not answer all the questions.

The Division of Epidemiology updated their literature review studies published since the 2013 review or published between December 2012 and January 2018. The aim of this updated literature review was to identify epidemiology studies that could advance our understanding of non-steroidal-associated cardiovascular risk with respect to whether a differential risk exists between products, vulnerable populations, risk factors, and time to event.

The Division of Epidemiology did not identify any new information to support labeling changes based on their review. And here's my conclusion slide and I would like to summarize what I've talked about.

The results from the PRECISION trial suggest that celecoxib carries cardiovascular risk that is no worse than the cardiovascular risk with ibuprofen and naproxen.

Additional cardiovascular, GI, renal, and all-cause mortality outcomes must be interpreted

descriptively. No new safety alerts were identified. Celecoxib did not adversely affect mean 24-hour systolic blood pressure. All outcomes must be interpreted in the context of the doses given in the trial. Thank you for your attention.

Clarifying Questions

DR. NEILL: Thank you. So we're a little early for a period for questions. And what I'd like to propose is that, at the morning session, there were at least two questions that were unanswered for which the sponsors have identified data, I think both for adjudication of the hypertensive admissions and for the inverse. Dr. Nissen, could you address those?

DR. NISSEN: Can you hear me? Yes, great. Let's have slide AH-5, please. We were asked about the characteristics for the inverse probability of treatment weighting for the aspirin analysis and so we have that slide for you. Here it is.

Seventeen characteristics were included in this propensity-weighting analysis. This is the aspirin analysis I showed you earlier. And you can

see what they are. And in gold, you see without the inverse probability of treatment weighting, without the propensity weighting, and then in blue triangles, you can see what happens after the weighting.

Obviously, the purpose of this was to try to balance these characteristics. And then the second question that was asked about adjudication, Dr. Blaha, I think asked for adjudication. That's slide AH-7. And I'll show you the definition that we use. This is from the manual of adjudication.

So you had to be hospitalized and with a diagnosis of hypertension, even if the duration of stay was less than 24 hours, does not include doctor office visits, and plus you had to have a blood pressure greater than 180 systolic or 110 diastolic with minimal or no end organ damage or a blood pressure greater than 180 over 110 with acute end organ damage defined as neurological symptoms, encephalopathy, et cetera.

That's unstable angina, acute MI, heart failure, or pulmonary edema. Renal damage is

exhibit by proteinuria, hematuria, acute renal failure, or aortic deception. So that was the formal definition of hospitalization or for hypertension. Those are my responses to your questions from this morning.

DR. NEILL: Thank you, Dr. Nissen. So I want to give ourselves time for clarifying questions for FDA. We've ended the FDA presentation a little early and so I'm going to use chair's prerogative to allow those of you that didn't get to finish with industry this morning to do so.

The questioners that I had in order were Dr. Tchetgen Tchetgen, Dr. Schmidt, Meisel, Hendrix, and Parker. So Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Dr. Tchetgen Tchetgen. This is for Dr. Nissen. Thank you for those additional information. I had a question actually about the inverse probability slide if you could pull that up again. And just a clarification; what was the aim of the analysis? What was the weight, the treatment that was using

the weight for? And that would be a little helpful in terms of what comparisons you're drawing in the analysis.

DR. NISSEN: Can I turn to our statistician, Kathy Wolski? She's going to help. Yes, there's a slide there.

DR. WOLSKI: Kathy Wolski, Cleveland Clinic. Can we get that slide up again? So this was looking at the effect of aspirin use, so the weighting was because aspirin was not a randomized medication in this trial. This was a way to try to balance the covariates between the aspirin and non-aspirin groups.

DR. TCHETGEN TCHETGEN: So this was not necessarily to also interrogate interactions, just the main effect of aspirin?

DR. WOLSKI: Also to look at the interactions as well.

DR. NEILL: Thank you. Dr. Schmid?

DR. SCHMID: Yes, this is Chris Schmid. I had a question about the meta-analysis slide, which I now can't find. So somebody might remember it.

There was a meta-analysis slide from the applicant. Maybe you can go on to the next person and I'll try to find it.

DR. NEILL: Will do. Dr. Meisel?

DR. MEISEL: Steve Meisel. This question may have been answered on this last clarifying slide. I'm not sure. But over the course of this trial, 10 years or so, our thinking on statins has changed quite a bit.

I'm wondering if there was any sub-analysis done for those people who were or were not on statins during this time and the impact of that on cardiovascular outcomes. That would be independent of the impact of the NSAIDs and/or the aspirin.

DR. NISSEN: That's a very reasonable question. Do we have the analysis? Yes.

DR. PRESSLER: Milton Pressler, Pfizer. I might be able to add just a little bit of clarity there. The use of statins, what I know about it, is that it was balanced across all the treatment groups. Roughly 50 some percent of the patients in each of the celecoxib, ibuprofen, and naproxen

groups were on statins.

I'll look at our statistician here. Did we do an analysis as to whether statin -- I don't know if we have an answer for your question as to whether that was a significant difference or not.

DR. MEISEL: I assume FDA didn't do that analysis, either. Right?

DR. LI: No, not on the statin use.

DR. NISSEN: It is an interesting enough question that we're going to go back and take a look at it.

DR. NEILL: Ah, academics. Dr. Hendrix?

DR. HENDRIX: Yes, Craig Hendrix. Was there any assessment of biomarkers, of thromboxane B2 or platelet function?

DR. NISSEN: That's a really great question. So we have a biomarker working group led by the group at Brigham, Peter Libby and then some others. And we are in the process of now thawing samples and we've got a whole bunch of biomarkers we're looking at. We simply haven't analyzed the data yet, but we find this of great interest as well

because we'd like to see if there are any biomarkers that predict who does and does not have any of the adverse outcomes that were observed with this class.

DR. HENDRIX: It'd be great if you could have it by noon tomorrow.

DR. NISSEN: We'll do our very best. I'll give you Dr. Libby's cell phone number and you can give him a call.

DR. NEILL: Dr. Schmid, I think you found what you were looking for?

DR. SCHMID: Yes, I did. Chris Schmid. This is MI-13. That's the slide. So my question is --

DR. PRESSLER: We'll try to get that up for you.

DR. SCHMID: -- there was a comment made about direct and indirect comparison and I just wanted to see; there was a number here that didn't make sense to me. So in the top two are direct comparisons if I understand correctly, where basically celecoxib is fairly similar to both

ibuprofen and naproxen.

Celecoxib has a higher risk compared to placebo as does ibuprofen, but naproxen doesn't. And the green, I believe, were indirect comparisons, which would suggest that they were combining the others with comparisons with celecoxib maybe.

So I wasn't quite sure why that was not a higher risk as the other two, higher risk.

DR. PRESSLER: We were just reporting or replicating the analyses that were done by the CNT group. So this is not our independent analysis. This is a report from their supplement. And the top part is their meta-analysis where celecoxib and ibuprofen or celecoxib and naproxen were compared in the same trials. That's a direct comparison.

The lower part, celecoxib versus placebo, was also direct because celecoxib had been studied in a number of placebo-controlled trials. For ibuprofen and naproxen, my understanding is that there was an imputation of what placebo would be from other trials where placebo was included.

Much of the data was derived from naproxen being compared to rofecoxib and then to placebo. So that was the indirect comparisons we're talking about and this was discussed at the last advisory committee, about this by Milton Packer about what was direct and what was indirect. And we were just reminding the committee of what was discussed at that time because our new data, which is now based on randomized controlled trials, aligns fairly well with the direct comparisons that were made in the study.

DR. SCHMID: The part that was confusing to me -- and it may just be because the indirect comparisons are different here -- is that celecoxib has a much higher risk than placebo, has a little bit lower risk than naproxen, but basically the same, which would imply to me that naproxen should be much worse than placebo. Yes.

DR. NISSEN: Yes. The problem is that, if you think of a triangle, so you compare A to B and then you try to figure out what's going on, comparing B to C. And so it's a very indirect

process. And the problem with the naproxen data -- and I think it led to a lot of the discussion about naproxen being cardioprotective -- is naproxen was studied primarily against rofecoxib and rofecoxib was the drug that seemed to have the worst outcomes.

So these indirect comparisons are very colored by the fact that the comparator wasn't celecoxib. It was rofecoxib. So when you then try to impute placebo, it makes naproxen look better than it actually is.

DR. SCHMID: Right, because if you actually did the indirect comparison with the celecoxib there only, you would get a much greater risk for naproxen.

DR. NISSEN: Yes. They didn't do that. They lumped all of the coxibs together and it was one of the objections we had to the analysis. And again, just please keep in mind the last slide that I showed, which showed the confidence intervals for CNT were really, really wide and they're much, much narrower, so we think we have a better answer.

DR. NEILL: Dr. Parker?

DR. PARKER: So my question relates to slide MC-8 and I just wanted to ask a little more about the visual analog scale and pain. This may have been addressed in the early FDA comments and I couldn't exactly understand it. I understand that you're showing in that slide -- do you want to pull it up? It's MC-8, if you can pull that up.

DR. PRESSLER: Just a moment. We're still stuck on the meta-analysis.

DR. PARKER: Yes. I get it. So I understand that that shows a change from the baseline. And if I heard correctly, that visual analog scale goes 0 to 100. And I wanted to ask the definition of clinical significance on that scale and also if you could help us understand rather than change from baseline what the actual numbers were for the OA and also for the RA cohorts. That's my first question.

DR. PRESSLER: Very good. So Dr. Cohen?

DR. COHEN: Sure. So again, most people feel that the minimally clinically significant

difference is somewhat greater than 10 millimeters. Okay? So there's some argument; 10 to 15, whatever, but that's what's felt to be clinically significant.

The baseline scores, if I remember correctly -- the statistician is here. We can put the next slide up. So the baseline scores were 54. I think they were a little higher for osteoarthritis than rheumatoid arthritis, 54 and 51.

DR. PARKER: Out of 0 to 100. And then the other question I had related to that was, can you tell me anything about the people in that who had analgesic rescue? How would I think about those that were also getting tramadol or opioids as analgesic rescue and interpreting those scores, just so I think about how I look at those?

DR. COHEN: I'll have to ask that question as well. Do we have that data?

DR. PRESSLER: In part, we have the data. The VAS scores were measured on the medications that patients presented with at the time of their

visit. And what we learned during the study is that, if patients had intolerable pain, then we had a rescue paradigm and many of those patients then were treated with opioids.

It amounted to something on the order of 25 to 27 percent of the patients. So I don't think we know what more than that because the measurements in this study on efficacy were not to validate the efficacy that was already known, but rather to just track how patients were doing on their pain during the study.

Maybe you can add some more.

DR. NISSEN: Yes. We included those when we had the discussions during the design because we really did want to know, were we giving comparable doses of the drugs. And that was always an issue here. And if I could have that last slide up with the baseline, not this slide, but the one before it, which shows the effect over time. It was not this slide.

Show us the change over time. The point I wanted to reemphasize is that -- yes, this is the

slide I wanted to show -- the efficacy for this therapy was fairly moderate. We looked at the literature as we were designing the trial and we agree that about a 10-point difference on a 100-point scale is the measure of clinical efficacy.

We needed to verify in the trial that we were actually getting that efficacy. In many ways, the efficacy of these drugs is moderate. I mean, it is significant, but it is really moderate. These people do hurt a lot and so, if you think about this, if you're on a 100-point scale and you go from 54 down to 42, you still have a lot of pain.

That's why 25 percent or so of the patients needed rescue.

DR. HERTZ: Hi, this is Sharon Hertz. I just have to interrupt a little bit and provide additional information about the behavior of patients in NSAID studies with osteoarthritis and rheumatoid arthritis.

In the absence of a placebo or some other superiority control, this could easily be

considered regression to the mean. And I think that, to say that there's this 10-point difference when there's absolutely no placebo comparator or any way to get assay sensitivity is overreliance on the data. The efficacy here is effectively similar.

Those p value differences that were on the slides, comparing the drugs; I don't know what those were intended to mean, but you can see this kind of change just for the regression to the mean and the placebo arm could have gone just as well.

DR. NEILL: Dr. Solga?

DR. SOLGA: Question for Drs. Hertz or Racoosin, just following up from before. I had the privilege of attending the 2014 meeting and that felt much, much different. There was also different kinds of evidence that were discussed. At the time, you had invited expert speakers, guest speakers from Oxford, Copenhagen, Philadelphia to speak about meta-analyses and randomized controlled trials, observational studies, biological plausibility, and the very best evidence from the

very best minds at the time were suggesting that Naprosyn was safer as a choice than other NSAIDs, including celecoxib.

In fact, EMA had already reached that conclusion and, as I recall, was not participating in PRECISION enrollment for the same reason. And so we had a rich discussion after so many presentations and this committee almost concluded the same. And then we discuss equipoise for PRECISION and we almost decided not to continue with the PRECISION trial.

As I recall, the FDA took a great risk, hung in there, and here we are today. And so I congratulate you on getting us from there to here. But I wonder, since today is really dominated by the PRECISION trial, when you consider the structure of today's agenda, did you think about re-inviting some of those speakers from 2014 to get other perspectives from different kinds of evidence?

Because I felt like, at the time, more than the cardiovascular safety of NSAIDs, what was at

issue was the different kinds of evidence being presented to the FDA and confidence therein. And as I recall, we spoke about it as perhaps the most investigated question in the history of medicine.

It seems like what we've concluded was that meta-analyses, observational trials, and biological plausibility, even when extremely well done by the most sophisticated methods by the best people, were perhaps incorrect.

DR. HERTZ: So rather than commenting on the conclusions from that meeting -- this is Sharon Hertz; sorry -- the purpose of that meeting was to further our understanding of cardiovascular risk in the context of all of the work that had been going on, all of the epidemiologic studies, all of those bits that had sometimes conflicting data, often had different methodologies, different countries with different standards and we always worry, when we're working in that environment, where there's some consistency but it's not always the case, whether there are underlying factors, underlying biases that we can't identify, that may be contributing to

the outcome.

So when possible, to get an actual study, prospective clinical trial, we try to do that. And we knew that this study was having challenges getting enough events in spite of a lot of effort on the part of the sponsor to really try and get the study populated.

So we thought it was important to see where we were with available information because there was so much work going on in the area. Now that we're here, really, the question is, what did we learn from this clinical trial and how should we think about these data? And how should that influence our thinking about appropriate labeling?

Ultimately, it will help clinicians hopefully make decisions about their own patient management. So to be perfectly honest, I'm not sure we actually know the mechanism. Garret FitzGerald aside, I'm not sure a lot of other people are confident that we know the mechanism. Is it blood pressure? Is it platelet? What is it? I mean, there's many possibilities and perhaps

there's many concurrent processes contributing.

Rather than sort of repeat that, we do think there's biologic plausibility, but now the focus really is this clinical trial and so that's why we designed this really to focus on that and not to have the larger discussion that we had then. And we only had one slide on the epi review that's been done, but we've been following this really carefully and our Office of Surveillance and Epidemiology has done a fair amount of work.

We just didn't think that there were different messages now in that area that needed to be presented other than to say nothing particularly different has arisen. So that's why the focus of the meeting is very different and is really about the clinical trial.

DR. NEILL: Thank you. So we've been able to, I think, get through clarifying questions for industry from this morning and beautiful segue. If there are additional clarifying questions for FDA, we have Dr. Lewis, Dr. Meisel, and Dr. Roumie, Dr. Ohman, Dr. Ho. Let's start with Dr. Lewis.

DR. LEWIS: In your presentation, you commented on the aspirin versus no-aspirin results. There's also, on page 78 of the Pfizer document, cardiovascular disease patients on and off aspirin. Both of those results still seem counterintuitive to the previous hypothesis and I wasn't sure if what you said explained all those pieces. Could you elaborate? I mean, it could be just subgroup analysis.

Is there a slide that you can point us to? Is this the statistical presentation or the clinical presentation? I'm sorry. So it's the presentation. I'm sorry, I can't say your name. Yes. So when she presented the aspirin/no-aspirin data, she made a comment that she thought that, that was explained by the fact that the naproxen and ibuprofen have some COX-1 inhibition themselves.

I didn't feel I understood it as a complete explanation for all that data. And also, as a corollary to that, if you break down the CVD patients to aspirin and no aspirin, you find again

a sort of counterintuitive result. Right?

Because the people who have cardiovascular disease and aren't on aspirin do better on Celebrex, it's just --

DR. HERTZ: So I'm going to start the answer and I think we'll have some others jump in. Okay?

DR. MEISEL: Could we put the slide up with that data?

UNIDENTIFIED FEMALE: Yes, it's slide 43 [indiscernible].

DR. LEWIS: Yes. And I don't know if Pfizer has a slide of that page 78 or something.

DR. RACOOSIN: Is this the one that you're speaking to, the one up on the screen, Dr. Lewis?

DR. LEWIS: Yes. I think she was on this slide when she commented on why she thought this sort of counterintuitive result. Remember, Dr. Nissen showed us?

DR. RACOOSIN: Right. Judy Racoosin. I think the point here is that what we've seen is, when patients are taking prescription dose, full, therapeutic doses of ibuprofen or naproxen, they

are inhibiting COX-1 and so they're functioning in a way as if even though they're interacting with the aspirin, they're still blocking COX-1.

So platelets are still being inactivated and, because they're taking it around the clock on their regular schedule, we're not seeing any of those washouts, what we saw earlier today about that risk.

DR. LEWIS: So are you saying these are some of your questions you're going to ask us in a way? But are you saying that what you're proposing, which I also still have a question about the other end of that, is that, because these drugs inhibit COX-1 themselves, then it's no big deal?

That's why I asked for on-aspirin Celebrex, which doesn't interfere with the binding of aspirin. Isn't any better because the drug's own hindrance of it is good enough? I mean, but then why is Celebrex a little better when you're not on aspirin?

DR. HERTZ: Right. So if you recall from this morning, when we looked at some of the studies

about the interactions, for instance the Gurbel study, and if we look at Dr. Hariharan's slides 13, 14, like around there, it's not exactly the situation. So that's aspirin alone and that's the level of thromboxane inhibition, assuming that's an adequate surrogate.

If you go to the next one, we have this combination where you see potentially some interference, but that's a very low dose of naproxen. One hypothesis to address your question is that, when you're on a full prescription dose of naproxen, you're already inhibiting the COX-1, thank you, and so you're sort of covered in a way, regardless of whether or not aspirin can find its way in to acetylate.

Now, the part of the question then becomes when does this interaction have a problem. So if you have use of an NSAID around the clock where your levels are falling below, then you've got periods of vulnerability. And if you're on a very low dose, that may be an issue, but also during the period when you're coming off the NSAID, but still

potentially blocking the aspirin.

So that's, I believe, what we were referring to, because, yes, you would sort of expect that, if the NSAID did not have the ability to inhibit COX-1 sufficiently to have this effect, then blocking the aspirin should have a more deleterious effect.

DR. RACOOSIN: Does that answer?

DR. LEWIS: It does, it does. I'm still a little confused by when the no-aspirin people, Celebrex wins. When does that happen?

DR. RACOOSIN: Right. I mean, the other thing to keep in mind is that patients were stratified to the three treatment arms based on what their baseline aspirin status was, but how patients were decided, who got aspirin, is not randomized.

DR. LEWIS: Right, wasn't randomized, right.

DR. RACOOSIN: So for the patients who were not on aspirin, we'd have to guess about why they were or were not because the whole idea of aspirin for primary prevention seems to be somewhat controversial. So we just can't go there.

DR. LEWIS: So kind of the lack of randomization and the fact that it's also kind of a subgroup might just limit how much it could tell us about combining these drugs.

DR. HERTZ: Or the lack of a standard definition for who should be on aspirin or not. I don't think we want to randomize the aspirin in the setting. We want to use it for very specific and consistent definition of a case. And that takes that variable out of the consideration.

DR. LEWIS: Yes. That'd be even in the two groups.

DR. NEILL: Dr. Meisel?

DR. MEISEL: Steve Meisel. Could you call up FDA's slide 16, please, from, I think it was, Dr. Li? It could have been the other afternoon speaker. No, not that one. It must be the other one.

DR. HERTZ: Hang on. Is it the mean individual dose slide?

DR. MEISEL: Yes. That's it. Can you explain how, in the ibuprofen, the mean dose for

osteoarthritis and SD is identical to that for RA? And the same is true with exception of a typo, it seems, for the naproxen. That fails the credibility test. And then maybe Pfizer can answer this question as well. I don't know.

DR. PRESSLER: Milton Pressler, Pfizer. Maybe we could help.

DR. LI: Excuse me. Bo Li from FDA. I guess this data we got from Pfizer, so Pfizer, can you explain that? That's a last-minute IR response for that, so I think Pfizer.

DR. PRESSLER: So first of all, just a point of clarification; the mean dose there that is listed has to be multiplied per times a day. So as we're reading across there, it's in the mean dose, 104 twice daily. So that's 208. 682, 3 times daily. I have to multiply in my head, something like 2,040. And then 426 twice daily is 852. So what transpired is that the osteoarthritis and rheumatoid arthritis patients dose-escalated about the same degree for ibuprofen and naproxen.

For celecoxib, they could not dose-escalate

if they had osteoarthritis because the approved dose was limited to 200 milligrams a day. They received a dummy. So it was a triple dummy design. So the intent was made to escalate, but they got a placebo, whereas in rheumatoid arthritis, where they could escalate the dose. Rather than getting a placebo, they got additional celecoxib.

DR. MEISEL: Right, but just the fact that the numbers are perfectly identical in the ibuprofen group for OA and RA, and virtually identical for the naproxen in the OA and RA, I mean, plus the standard deviations being the same. There's something weird about that.

DR. PRESSLER: It's just, again, about 55 percent of the patients had intent to dose-escalate. Again, maybe Dr. Cohen can explain how much pain these patients have, but we were selecting patients that had chronic pain in order to have the equipoise to do the study.

DR. NISSEN: You raise a good question. Overnight, if you will, we're going to take this back. And we have a lot of the data on a computer.

And let us make sure that this is not a mistake. Your point is well taken. We'll take a close look at it and we'll tell you what we find.

DR. MEISEL: Thank you.

DR. NEILL: When I consider the occurrence of random events in the world and that this is 2018, did I mention I'm from Philadelphia? The Eagles have won the Super Bowl. It can happen, is all I'm saying. But I appreciate your looking at the data.

DR. MEISEL: How about those Phillies here?

DR. NEILL: Dr. Lewis, if I could get you to turn off your microphone, we're going to go to Dr. Roumie, who is next.

DR. ROUMIE: Christianne Roumie. The question is for Dr. P. I'm just going to not try to butcher your name. In slide 15, you mentioned that the protocol required that patients discontinue the drug on the day of their APTC event, but then reported 20 percent really did continue the drug more than 31 days. And there were recurrent events. I did not see any

information about whether those recurrent events were differential by study arm or if that has even been looked at.

DR. POKROVNICHKA: We have a slide that we are going to show you, what happened, and we have a backup slide, 51, please, from the clinical presentation. Row 8 says second APTC event on treatment, days to treatment discontinuation. It shows you the 4 people who experienced the second APTC event.

They didn't stop taking study drug after their first APTC event. There were 4 people. We don't have the treatment arm that they were on. It was just 4 --

DR. HERTZ: Yes. the number was so small. We just didn't think that an analysis by treatment group was really going to be meaningful.

DR. ROUMIE: I mean, I get that, but I think, when we think of things from a population standpoint and the quantity of ibuprofen and Naprosyn that's used over the counter, many patients don't think to stop those medications once

they have a significant event.

So that's one of the things that I think we're being asked to consider.

DR. HERTZ: So, as with Dr. Nissen and his group, we shall go back and look at what treatment group those 4 people were on.

DR. NEILL: Dr. Ohman?

DR. OHMAN: Yes, Dr. Ohman here. Dr. Li, on slide 8 that you presented on the confidence intervals, upper boundaries, how did you arrive at this 1.33? What prior arc did you actually used to come to this boundary? Because when we deal about risk, it's an interesting question. How much does the population accept of risk? Obviously, as pointed out by Dr. Nissen, you all helped him in coming up to this boundary.

DR. HERTZ: My recollection -- this is Sharon Hertz -- from way back when is we were trying to navigate having an amount of risk that we thought we could tolerate and not consider it hugely different versus the feasibility of actually ever getting a study completed.

When we started, as you heard, people were not doing as well in terms of cardiovascular outcomes in general. And when the event rate was lower than expected, which is of course good from a public health perspective. I'm not bemoaning that.

But really, a part of it was practicality. We couldn't get the perfect study. We got a study that we thought would be informative in a meaningful way. So it wasn't based on, like, a set of data, or a set of articles, or something very specific I can point you toward.

DR. NISSEN: May I comment?

DR. NEILL: Yes, Dr. Nissen.

DR. NISSEN: So we had a lot of discussions internally on the executive committee. We had discussions with the sponsor. And I remember just like it was yesterday even though it was more than 10 years ago.

We went into the FDA and we actually laid out the 1.33. And there was a good back and forth with FDA about all this and we showed what it would take, how big a trial, et cetera.

This was a practical approach. We made that initial proposal. We had discussions in that range, in a week at 1.3, 1.33, et cetera. And the other insight was not so much what the upper confidence interval is, but what would be the tolerable point estimate?

We thought on the executive committee that more than a 12 percent excess, given how many people take these drugs, being able to rule out at 12 percent excess, not having a 12 percent excess on the point estimate, was a reasonable standard for public health.

FDA accepted that and gave us feedback about it. And we had a very good dialogue on it. But there's no magic in this. As you know, with non-inferiority studies, there's no magical way to do it. We just tried to do what was practical and what we thought would be clinically meaningful to the medical community.

DR. NEILL: Thank you. Dr. Ho?

DR. HO: Yes. This is Michael Ho. I had a question on slide 28 and this is for Dr. Li. I had

a different slide. This is a slide, death by trial period.

DR. POKROVNICHKA: Clinical 28.

DR. HO: Yes. So I guess I'm struggling on how to interpret this or what the message for the committee is of this slide. I mean, it seems like most of the deaths occurred after patients discontinued their drugs for 30 days.

DR. POKROVNICHKA: So when we looked at the data, the way Pfizer considered double-blind and follow-up was the double-blind period and follow-up period included these 30 days after study drug discontinuation.

After we looked at the incidence rate, it just appeared that you have less chance of dying if you are taking a non-steroidal because the incidence was high during the follow-up period.

Then we broke it down into the double-blind period where patients died while on study drug and 30 days after the study drug was discontinued. And then the continued follow-up after this initial first 30 days after the study drug was

discontinued. So the highest incidence of that actually occurred during death 30 days after the study drug was discontinued.

Now, the leading cause was cardiovascular event. And we were trying to figure out why patients were dying primarily within these 30 days after the study drug was discontinued. And what we wanted to look at was what was the reason for them to discontinue the study drug? Maybe there was the answer.

When we looked at what was the reason, turned out that we were expecting to see the reason for study drug discontinuation to be an adverse event, so something happened to them, and that's why they stopped the study, drug and soon after, they died.

When we looked at that, it turned out that the reason for stopping the study drug -- and we're talking only about these people who died during the 30 days after the study drug was stopped -- very few, if you look at just the numbers, 4 for celecoxib, 1 for ibuprofen, and 3 for naproxen

discontinued the study drug due to an adverse event.

However, for the majority, if you see, 22 for celecoxib, 35 for ibuprofen, and 27 for naproxen; the reason for discontinuing study drug was recorded as death. And when we asked Pfizer to clarify how did this happen, apparently investigators were instructed to record the reason for study drug discontinuation as death if the death occurred within a few days when the study drug was discontinued.

So the actual reason for why the study drug was discontinued was not recorded because it was recorded as death. Now, how many of these reasons were adverse events or others, there's just no way to figure out.

DR. HERTZ: So just to emphasize what --

DR. NEILL: Dr. Hertz, just a moment. For the benefit of the transcriptionist, the former speaker was Dr. Pokrovnichka, not Dr. Pratt. Go ahead, Dr. Hertz.

DR. HERTZ: So just to clarify or emphasize

that last point, instead of capturing the reason for discontinuing study drug as the proximate reason on the day the decision was made, if somebody died within a few days of that, they were counted as death as the reason for study drug.

So it's not that 22 people on celecoxib in that 30-day period just died and that was the same day study drug was discontinued. Some faction of them, some proportion had some event, some decision to stop study drug and then they died within a few days.

So it's just data that we haven't finished picking through exactly yet. So part of the reason why we look at this period is because of that transition effect of COX-1 inhibition that we were looking at earlier and we want to see when someone first comes off their NSAID.

We were worried that that's a period of great vulnerability. Most of these were fairly early, we think, but that's why this is sort of a funny slide.

DR. HO: Yes. I guess it would be

interesting to see if those events defer whether patients were on background therapy of aspirin or not. But I guess the other thing that was interesting to me was just most of the events in all three groups were 30 days after they discontinued drug.

DR. POKROVNICHKA: Yes, exactly. That's why it was --

DR. HERTZ: It was within 30 days of discontinuing. It wasn't on day 30. It was within the first 30 days of following drug discontinuation. And we're still working on this. You can see we found this number. We thought it peculiar and we asked for some additional information, which we didn't get that long ago. So we're still sorting through that.

DR. NEILL: So it's now 3:30. I've got three committee members who are still looking to ask a question. What I'm going to suggest is that we take a break. We have another period for clarifying questions after CPHA presentations shortly. And we'll begin with those for

Dr. Tchetgen Tchetgen, Robotti, and Rosenberg. So we'll now take a 15-minute break.

Panel members, remember you should not discuss the meeting topic during the break, amongst yourselves, or with any member of the audience. We will resume at 3:45 p.m.

(Whereupon, at 3:30 p.m., a recess was taken.)

DR. NEILL: Good afternoon. It is now 3:45 and we will now proceed with additional industry presentations beginning with the Consumer Healthcare Products Association.

Industry Presentation – Barbara Kochanowski

DR. KOCHANOWSKI: Good afternoon. Thank you for the opportunity to present today. I'm Barbara Kochanowski and I head regulatory and scientific affairs at the Consumer Healthcare Products Association. CHPA is a member-based trade association representing the leading manufacturers and marketers of over-the-counter medicines and dietary supplements.

Our membership totals more than 200

companies. CHPA has been serving the self-medication industry since 1881. As one of the oldest trade associations in the U.S., we're a strong advocate for consumer healthcare products industry and provide leadership and guidance on regulatory and scientific issues.

Today I'm going to discuss some important information on OTC analgesics and their labeling. I'll also talk about the CHPA educational foundations, efforts to educate consumers about safe and responsible use of OTC medicines and a very new program focused on internal analgesics.

OTC medicines are a critical component of self-care. They empower consumers, cut costs, and improve health and well-being. OTC medicines are the trusted first line of defense for more than 240 million Americans who use them every year.

OTCs are by their very nature accessible, affordable, trusted, and empowering. There is a high consumer demand for OTC analgesics with pain being the most common condition treated with an OTC medicine. The market is large and, in turn, OTC

analgesics contribute significant savings to the U.S. healthcare system.

Consumers have a variety of choices for their self-treatment of pain. Each of these options has benefits and different attributes as well as risks that are included in the product labeling.

These drugs differ in their pharmacodynamic and pharmacokinetic properties and therefore should be evaluated individually. Two of these drugs were studied in PRECISION, albeit at higher doses and for chronic conditions versus OTC use. And you'll hear more about ibuprofen shortly.

Aspirin is unique in that it is used for pain relief, but also for cardioprotection. And the OTC product is purchased for both of these uses. The drug facts labeling only addresses treatment of pain. Details related to cardiovascular benefits are included only in professional labeling.

However, on November 6th in 2017, FDA released guidance regarding the use of

cardiovascular-related imagery on labeling and packaging of OTC aspirin products. The guidance recommends that OTC aspirin products that have such images include a statement reminding consumers to discuss the use of aspirin with their doctors before taking the OTC product as prevention for cardiovascular events.

The review of NSAID safety, including possible aspirin interactions, has been ongoing since the late 1990s. Evidence supporting potential risk has largely been derived from two sources; long-term treatment of chronic disease with prescription NSAID doses and in vitro ex vivo platelet aggregation studies.

The clinical significance of these two lines of evidence as well as the relevance to OTC use has not been established. Nonetheless, as the result of the FDA Healthcare Professional Communication in 2006 and the advisory committee meeting in 2014, changes related to cardiovascular risk and aspirin interactions have been made to OTC labeling for non-aspirin NSAIDs.

The discussion in this meeting revolves around the new data since the last advisory committee meeting, including PRECISION, and new data with respect to naproxen-aspirin interactions. The new labeling with respect to cardiovascular risk was an outgrowth of the 2005 and 2014 advisory committee reviews and was extended to all prescription and OTC NSAIDs.

Aspirin interaction labeling was based on data available at the time and was limited to ibuprofen. Based on lack of consistency in the aspirin interaction findings with naproxen at the time, no label recommendations were made for naproxen.

This slide shows the heart attack and stroke warning on OTC ibuprofen and naproxen. The CV risk is very clearly stated. This slide shows the OTC labeling on ibuprofen, warning about potential impairment of aspirin's cardioprotective effects.

The consumer is instructed to ask their doctor or pharmacist before use if they are taking aspirin for heart attack or stroke and the FDA has

provided a science paper that healthcare professionals can use to advise patients and consumers on the appropriate concomitant use of ibuprofen and aspirin.

With respect to OTC use conditions, it's important to recognize the limitations of the available data, generated under prescription use conditions of high dose, long duration, and chronic pain.

The relevance of the aspirin interaction studies to CV outcomes has not been clearly demonstrated. Current OTC labeling reflects extrapolation and judgment based on the available data. Available data suggests there's no increased cardiovascular risk when OTC formulations of these agents are used as directed.

To supplement the internal analgesics manufacturers' efforts to ensure the safe use of their products, the CHPA Educational Foundation also provides valuable information to consumers on how to responsibly use all consumer healthcare products, including OTC analgesics.

The CHPA Educational Foundation is the philanthropic, nonprofit arm of CHPA and shares the same vision as the association, always putting the consumer first, creating happier, healthier lives through responsible self-care. Its mission is to be the trusted source of education for consumers in three distinct areas; how to use, store and dispose of OTC medicines and dietary supplements safely and responsibly.

So how does the foundation reach consumers? In two key ways. The first is through its consumer-facing brand, knowyourotcs.org. The website provides information for consumers making OTC decisions wherever they are, be it at the pharmacy aisle or by their child's bedside. The website is a one-stop destination featuring an expanded ingredient index, a medicine label reader, physician authored, expert content, downloadable materials, and useful tips on safe medicine use, storage, and disposal.

The second way we reach consumers is through the foundation's national educational campaigns.

The foundation works with more than 60 organizations, including government agencies, professional societies, consumer health groups, and industry associations on educational campaigns and initiatives that address specific areas where consumers need guidance and support.

From left to right, these are our current campaigns. Treat With Care educates parents with young children about how to safely use pediatric cough and cold products. Up and Away educates parents and caregivers about safe medicine storage in partnership with the CDC and its PROTECT Initiative.

Know Your Dose educates consumers about how to safely use acetaminophen in partnership with the Acetaminophen Awareness Coalition. And last, OTC Pain Reliever is our newest initiative and addresses the safe use of the broader, internal analgesics category.

Last year, the foundation launched this pilot campaign aimed at increasing consumer knowledge about the different categories of OTC

pain relievers, encouraging appropriate selection and safe use.

The pilot featured a digital media campaign that directed consumers to read the drug facts label and visit a new interactive pain page on KnowYourOTCs.org that provides a step-by-step educational journey to better understand the different OTC pain relievers available on the market today and some of that content is shown on the screen.

We look forward to continuing these efforts and working with healthcare providers as well as other stakeholders to ensure these valuable medicines are part of the larger pain conversation.

To summarize, OTC analgesics are an important contribute to the health and well-being of Americans. They are widely used for an array of self-treatable conditions and have demonstrated a favorable safety profile over decades of use. Safety is continuously monitored and no new signals have emerged that question the favorable benefit-risk of OTC analgesics.

Our members are committed to working with FDA to provide appropriate labeling. Our educational efforts will continue to incur safe and responsible use of OTC pain medicines. CHPA and our member companies are appreciative of the opportunity to share our perspective today.

We thank you and we welcome any questions you may have after the J&J presentation. Thank you.

DR. NEILL: Thank you. Dr. Kuffner?

Industry Presentation – Edwin Kuffner

DR. KUFFNER: Good afternoon. I'm Ed Kuffner, chief medical officer for Johnson and Johnson Consumer. J&J Consumer markets Motrin, which contains ibuprofen. Today in the U.S., Motrin is only available OTC. I'll focus my presentation on the cardiovascular safety of over-the-counter ibuprofen, including concomitant use by patients and consumers taking aspirin for cardioprotection.

Ibuprofen's CV risk is dose and duration dependent. Since OTC doses and OTC duration are

lower than prescription, the CV risk of OTC ibuprofen is lower. The cardiovascular risk of ibuprofen when taken according to the OTC label is low.

The approved OTC ibuprofen label has many CV warnings and directs those taking aspirin to consult a doctor before use. I'll review the label in a few moments.

Ibuprofen is an important OTC medicine. Last year, about 40 percent of U.S. households purchased single-ingredient ibuprofen. Approximately 17 percent of adults take ibuprofen each week. In the U.S. ibuprofen has been available OTC for over 30 years.

We recommend it to patients, use it to make children feel better, and most of us probably take it ourselves. Patients and consumers benefit from OTC access to a variety of pain medications.

The OTC ibuprofen label is designed for short-term use of lower doses. OTC ibuprofen is indicated for temporary relief of minor aches and pains as well as fever. Prescription ibuprofen is

indicated for relief of mild to moderate pain and more chronic conditions such as RA and OA.

The OTC label instructs stop use and ask a doctor if fever or pain gets worse or persists. OTC ibuprofen is labeled for a maximum of 10 days of self-use. The OTC tablet strength of 200 milligrams is different than the prescription tablet strength of 400, 600, and 800 milligrams.

The OTC 200-milligram tablet is more conducive to taking the lowest effective dose and that's what the OTC label recommends. Finally, the 1200-milligram maximum OTC daily dose is approximately a third of the prescription maximum dose.

In 2014, this committee and FDA reaffirmed that the benefit-risk of OTC ibuprofen remained favorable. There was agreement that some changes to the OTC label would be appropriate.

Let's look at the changes that were part of OTC NSAID class labeling. The OTC label now contains a heart attack and stroke warning. The heart attack and stroke warning incorporates

language that was previously on the label about not using more than directed or for longer than directed.

The new warning added the concept of NSAID class risk, changed "may increase" to "increased," and added the term "heart failure." This warning is more prominent. Stroke was added to the list of conditions in the "ask a doctor before use" section.

The previous OTC label told users to stop use and ask a doctor if any new symptoms appear. And this very important warning remains on the label. The new label goes a step further, identifying specific symptoms of heart problems or stroke, including chest pain, trouble breathing, weakness in one part or side of the body, slurred speech, and legs swelling.

It's important to understand the OTC label already has lots of information aimed at decreasing cardiovascular risk, especially in vulnerable populations. It states, "Do not use right before or after heart surgery."

In addition, the label states, "Ask a doctor before use," in three very important situations; if you're taking aspirin for heart attack or stroke because ibuprofen may decrease this benefit of aspirin, if you are under a doctor's care for any serious condition, or if you are taking any other drug.

We wanted to better understand to what extent proposal follow OTC dosing directions. We worked with experts -- Dr. Kaufman and Dr. Shiffman, both of them, are here today -- to conduct a study on real-world use of ibuprofen and other NSAIDs.

Thirteen-hundred and twenty-six ibuprofen users filled out an online diary for one week. They were not required to know that the medicines they were taking were NSAIDs. Ibuprofen users were defined as those taking the medicine within 30 days before the study and also at least once during the diary week.

Subjects picked all NSAIDs they took from a list and recorded how much and at what time they

took it. Exit surveys asked questions about medical history, knowledge of the NSAIDs taken, and attitudes about medications.

Data on both users and dosing days were collected and analyzed. 88 percent of over-the-counter ibuprofen users did not exceed the maximum labeled over-the-counter dose. On the graph, you see the percent of dosing days with OTC ibuprofen on the vertical axis and doses in milligrams on the horizontal axis.

On 91 percent of over-the-counter ibuprofen dosing days, users did not exceed the maximum labeled OTC dose of 1,200 milligrams labeled in red. In fact, on 55 percent of the dosing days, 400 milligrams or less was taken. This is real-world use.

The dosing patterns studied in PRECISION were not typical of OTC ibuprofen use. We heard Dr. Nissen talk about that. In PRECISION, the mean daily dose was 2,045 milligrams and the mean duration of use was over 20 months.

In real-world use of OTC ibuprofen, the

average PRECISION dose occurred in less than 1 percent of users and the median duration of use was less than 2 days. In fact, 75 percent of OTC users took ibuprofen for less than or equal to 3 consecutive days.

In these data, we see opportunities to bolster our educational efforts. Real-world use revealed concomitant use of ibuprofen and other NSAIDs, including aspirin. You saw this in the PRECISION data as well.

During the diary week, 19 percent of ibuprofen users took more than 1 ibuprofen product. 37 percent of ibuprofen users also took a non-ibuprofen NSAID. And 17 percent of ibuprofen users took aspirin for cardioprotection.

Let's look in more detail at the use of aspirin for cardioprotection. I'll try to put the real-world data into context, especially as it relates to some of the pharmacodynamic data that was presented earlier today which discussed the timing of aspirin use as well as the timing of ibuprofen dosing.

As I said, we have data on both users and dosing days of when people took ibuprofen and aspirin. As noted, 17 percent of ibuprofen users took aspirin for cardioprotection at some time during the diary week. For those 50 plus, this increased to 32 percent.

We sought to better understand a potential cardiovascularly relevant drug-drug interaction between ibuprofen and aspirin. Our data allowed us to determine when ibuprofen was taken within 8 hours prior to or within the same hour as aspirin.

This timing occurred on 27 percent of the days when aspirin was taken for all ages and a bit lower on 22 percent of the days among those 50 plus.

How this timing may potentially affect cardioprotective benefit of aspirin is unknown, but these data provide some context of real-world use.

We also see in this real-world example opportunities for education. J&J Consumer has a strong commitment to educating patients, consumers, and healthcare professionals. We've been doing it

for years. Our goal is to encourage proper and safe use of ibuprofen and other medicines.

Our approach is scientific, collaborative, and iterative. We often test various messages to determine the approaches that are more likely to change behavior. We work with a broad range of stakeholders, often sharing validated messages so we're all using a common language to drive behavioral change.

I'll show you a few examples. Our research has shown that patients and consumers are more likely to heed messaging if we give them context, such as why it's important and how to do it.

Here's an example from the Get Relief Responsibly campaign. We tell people to take the smallest effective dose and take it for the shortest amount of time needed. And we tell them why, because the chance of harmful side effects increase the more you take and the longer you take it.

We tell people to only take one medicine containing an NSAID at a time. We give them some

additional information. More than 900 over-the-counter and prescription medicines contain an NSAID. Most people are surprised by that number and that's the aha that really gets people to pay attention.

We encourage people to maintain the benefit of aspirin heart therapy by being aware that ibuprofen may decrease this benefit. And we consistently reinforce the message of always reading and following the label and, if you have any questions, following up with healthcare professionals.

Here's another example. Through research, we know that people may not realize that aging, changing health status, and taking new medications can change their health risk, even with familiar over-the-counter medicines they've been taking for years.

Here, you see the "some things just don't fit the way they used to" messaging (phonetic). It lets people know that, while certain warnings may not have applied when they were younger, they may

apply now. It's a good lesson for all of us.

We certainly can't expect patients or consumers to know what's on the drug facts label and its importance if we don't teach them. The OTC Scholastic Medicine Safety program is based off of FDA's Medicines in My Home program. In 2017 alone, this program reached over 400,000 teachers and school nurses and taught countless teens and pre-teens about the drug facts label and safe medicating behaviors.

This initiative is having real public health benefit. In summary, the cardiovascular risk of ibuprofen when taken according to the OTC label, is low. The PRECISION trial, while important, is of limited applicability to OTC ibuprofen, which is labeled for different indications, lower doses, and shorter duration. We heard that this morning.

The OTC label warns about CV risk and directs users with CV risk factors to consult a doctor before use. The OTC label further informs aspirin users to consult a doctor before use as well.

I'll close by addressing the three FDA questions relative to OTC ibuprofen that this committee has been asked to discuss. Let's start by addressing discussion question number 5. We agree with FDA that data support a pharmacodynamic interaction between ibuprofen and aspirin.

The dose, timing, and individual's underlying CV risk likely influenced the clinical relevance of such an interaction. Although we are not aware of randomized clinical trials with CV outcomes that specifically address this topic, we can't rule out a clinically relevant interaction for some patients.

Healthcare professionals are in the best position to provide individual patient guidance. That's why the OTC ibuprofen label appropriately states, "Consult a doctor before use if taking aspirin for heart attack or stroke because ibuprofen may decrease the benefit of aspirin."

Let's now address discussion question number 6. There likely are patient populations for whom the risks of concomitant use with aspirin may

outweigh the benefits of ibuprofen. Healthcare professionals are, again, in the best position to provide individual patient guidance.

Please remember that cardioprotection is not an OTC indication for aspirin. Patients using aspirin for cardioprotection should be under the care of a doctor. The current and approved OTC label for ibuprofen states, "Do not use right before or after heart surgery."

It also instructs those with cardiovascularly relevant conditions to ask a doctor before use. These conditions on the label include high blood pressure, heart disease, stroke, under a doctor's care for any serious condition, or taking any other drug. It's hard to think of a vulnerable population not covered by these broad warnings.

This brings us to the voting question, number 9. And one of the most important recommendations you will make that will impact patients and consumers, healthcare professionals, and the interactions we have with our patients.

Adding a contraindication to the OTC label would be overly restrictive, potentially confusing, and could have unintended consequences. Data suggests that taking immediate-release aspirin 30 minutes before a 400-milligram dose of ibuprofen is likely to maintain aspirin's cardioprotective benefit.

This situation certainly does not meet the definition of a contraindication. For a contraindication, the risks should outweigh any possible therapeutic benefit. There are instances where a healthcare professional, myself included, might instruct a patient on aspirin for cardioprotection to take an OTC dose of ibuprofen.

It may be the best option for some patients and their doctor would be in the best position to assess the benefits and the risks and counsel the patient appropriately. A contraindication on the OTC label puts healthcare professionals in a difficult situation where they should never recommend ibuprofen to any patients taking aspirin for cardioprotection.

This is not consistent with our understanding of the data that we heard this morning. It runs counter to our collective goals of encouraging patients and consumers to always read and follow the label and involving healthcare professionals in important benefit-risk discussions.

The current approved ibuprofen label, which recommends consulting a doctor before use if taking aspirin for heart attack or stroke, is most conducive to achieving these goals. Thank you very much and I am happy to take any questions.

Clarifying Questions

DR. NEILL: Thank you, Dr. Kuffner. We now have another period of time set aside for clarifying questions. I've got three questioners left over from our prior period, to which we're going to add Dr. Farber as a fourth. If any of you have questions that have arisen, there's Dr. Cunningham in between. Just get our attention. Dr. Tchetgen Tchetgen?

DR. TCHETGEN TCHETGEN: Eric Tchetgen

Tchetgen. This is a question addressed to, I guess, the FDA team. It's clear, given the results that were presented this morning, that there are a lot of challenges with non-inferiority designs, most of them having to do with post-randomization events, therefore, that compromise, the opportunity to exploit randomization to address possible sources of bias.

You presented some analyses that dealt with dropout or missing data. I wonder if there were additional analyses that were explored to deal with discontinuation. I mean, it's very hard to interpret lack of evidence against non-inferiority. That's a double negative. It's really hard to disentangle, but to be able to reject non-inferiority if you have basically 70 percent discontinuations and 30 percent adherence rate essentially.

These events were post-randomization, but they were also in a continuum. Adherence as I understood it happened over time, but the analysis tended to really discretize and simplify the data

as opposed to treating them like an observational study.

So this is a long question. But the broad question is, is there an opportunity to really analyze this data as they should have been longitudinally using observational methods to account for post-randomization events, sort of using the state of the art.

DR. LI: This trial, because of the pain condition treated, I think is challenging to keep the patients on treatment. Though we looked at this discontinuation of treatment, they all looked balanced across the arms. I think we keep the ITT analysis and the mITT analysis both in the primary criteria to be met.

So one reason is because ITT analysis may have the problem you mentioned, that it's that observational study. It includes those off-treatment events. But we did not use those, like matching method used in the observational study, to analyze, to do sensitivity analysis for PRECISION.

DR. TCHETGEN TCHETGEN: So just one

clarification; so my understanding is, intent-to-treat analyses for non-inferiority design is not quite the same thing as in superiority design. You don't have the same statistical guarantee that you might get a false, that your type 1 error would be controlled.

DR. LI: Right.

DR. TCHETGEN TCHETGEN: So neither ITT nor mITT in this particular application is conforming [indiscernible]. It will in fact be in the favor of, in this case, not finding a signal. And so in this context, I think one might entertain further exploration of what actually occurred post-randomization as it becomes more and more relevant.

DR. LI: I agree with you that the ITT analysis is not like the efficacy analysis because ITT analysis is more conservative for the efficacy claim. But it's not for the safety because we want to test non-inferiority. It may bring in a dilutional effect for these off-treatment events. That's why we also think the mITT analysis is important.

DR. NEILL: The irony of me being the person trying to decide between two statistician discussing things that I'm not sure about. Later, we'll chat about conforting and some of these concepts. Has your question been answered, Dr. Tchetgen?

DR. TCHETGEN TCHETGEN: Yes.

DR. NEILL: Ms. Robotti?

MS. ROBOTTI: Hi, Suzanne Robotti. I actually have, I think, very straightforward simple questions on two charts. I just want to make sure that I'm understanding them correctly. The first one is page 28 from the FDA presentation, I think Dr. P.'s presentation, the one right after general safety.

It was already up on the podium. Yes, there you go. And so just remember I'm a layperson. So going across one of the top lines there, DB is double blind, so that's during the trial period, 30 days after the drug is discontinued, and then FU is follow-up, yes? And that's an extended period for how long?

DR. POKROVNICHKA: Until the patient stayed in the study. So DB is double blind. It means that the patient was on study drug. And then at some point they stop the study drug for whatever reasons and the 30 days captures the 30 days immediately after the study drug was discontinued.

The follow-up is until the patient stayed in the study off drug. So they stopped study drug, but the follow-up that we have on this table excludes the first 30 days off follow-up after study drug was discontinued.

MS. ROBOTTI: Where does it exclude the middle column?

DR. POKROVNICHKA: The middle column includes only the 30 days of follow-up after study drug discontinuation.

MS. ROBOTTI: Right, and then after that, on day 31, they fall into the follow-up group for whatever period of time, great.

DR. POKROVNICHKA: Yes.

MS. ROBOTTI: So down to the second to the bottom line, once again, you've got death. And the

reason for the drug discontinuation is death and you understand that that's because of the crossover period. Doctors, for the couple days, just put them in the --

DR. POKROVNICHKA: Doctors were instructed to list the reason for study drug discontinuation.

MS. ROBOTTI: Right. So the 66 people in the follow-up discontinued because they were dead and then they died afterwards. Am I misunderstanding this again? They seem to be dead. So why are they dying again?

DR. HERTZ: So this is Sharon Hertz. There was a peculiar thing in the attribution of the reason for study drug discontinuation. That's not the norm in most clinical studies. If somebody died within a few days of stopping their study drug, even if they were alive when they stopped their study drug, they were counted as a death when that occurred in this post 30-day period.

The reason why we look at this period is because we want to look at the period of time when people are coming off an NSAID and they may be more

vulnerable to the effects of not having as much COX-1 inhibition.

MS. ROBOTTI: Right. You can see on the previous chart it dropped the day after.

DR. HERTZ: So in this 30-day period, there were a large number of deaths relative to the other study drug period, but --

MS. ROBOTTI: But I'm asking about the follow-up period.

DR. POKROVNICHKA: Maybe Pfizer can answer this question, why the reason for study drug discontinuation, for study drug discontinuation in the follow-up period.

MS. ROBOTTI: I understand it for the 30-day period, but I'm confused about the follow-up.

DR. POKROVNICHKA: Yes. If it was within a few days, but then we are falling into a category when it was beyond 30 days. Was similar instruction given to the investigators for recording the reason for study drug discontinuation?

DR. PRESSLER: So excuse me. This is Milton

Pressler, Pfizer. I can explain a couple things, but I'm also confused by the table. Part of the follow-up we do for every clinical trial is, when patients withdraw from treatment, we continue to track them for 30 days. That's part of the regulations.

In this trial, we were desiring to try to track the patients for as long as possible to try to ensure that we got good follow-up of patients who had once taken an NSAID. So we were looking to try to follow the patients for as long as possible.

We analyzed the data by intention-to-treat, which meant that, if a patient stopped taking the medication, we continued to track them and what happened to them. But the issue is, downstream from after they've stopped the medication, what's going on with them may be their underlying disease or it may be their medications. No one knows.

So that's why we also analyze based on this modified intention to treat, where the analysis is done on just the patients that are continuing on the medicine. Now, our statistician may be able to

clarify further. I don't know if you want to or not.

We had a slide, I think, that showed ITT over 30 months or 42 months and I don't know if that's helpful or not, but I can't see it.

DR. NEILL: If you could speak into the microphone, please.

MS. ROBOTTI: I'm sorry. It's Sue Robotti again. So I don't mean to be pedantic. But if you look under the follow-up column, there were 135 deaths in the follow-up period, whatever period that was, day 31 plus.

Then I thought it was very great that the FDA said, well, what were the reasons that the person stopped taking the drug? Because maybe it was an SAE or something like that. And you've got this funny line down there that says death.

We've explained why death is in the 30 days after drug. I don't understand the people. The reason they stopped taking the drug was because they died, 66 of them, but yet they also died in the follow-up period.

DR. PRESSLER: No, no, it's not the same people.

DR. POKROVNICHKA: I can explain or figure it out.

MS. ROBOTTI: Good, thanks.

DR. POKROVNICHKA: This 66; let's take just celecoxib, 66 people in the follow-up. We had to hit enter, so the 66 will go under other.

MS. ROBOTTI: It's the wrong line.

DR. POKROVNICHKA: Yes, similar for the follow-up.

MS. ROBOTTI: That's a lot of people for other. I thought you said miscellaneous, but I think -- yes, okay.

DR. POKROVNICHKA: It's for all other. All other could include that we don't know how many of those, but just take it as all other.

MS. ROBOTTI: All other. Got it. That was a much shorter answer.

DR. POKROVNICHKA: For the 30 days' follow-up, what you say is correct.

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: I guess my question was more a comment following regarding this table and discussion with my clinical trialist colleagues here. We think it's just a common occurrence in clinical trials, kind of a reverse causality association that you find an increase just after discontinuation, because I think that was mentioned. Patient discontinued for some reason set out related to treatment or to their condition. They get sick, they have something occurring, they get home, and so that the physician discontinues the treatment, that they may die.

So I don't think it -- most of the time, it has nothing to do with the treatment.

DR. NEILL: Dr. Farber?

DR. FARBER: So this is for Dr. Kuffner and, if you could put up slide 8, I have two questions, if you could put up slide 8 first. So I wonder, in terms of asking the doctor or pharmacist, I wonder if you have any data on the percent of physicians who understand things like pharmacodynamics and the interaction between aspirin and NSAIDs regarding

cardiovascular disease on the one hand.

Then on the other hand, any information about the percent of physicians who engaged in a lengthy discussion with their patient about such issues, being a general internist and knowing the data on patient-physician communication, I think that's uncommon.

DR. KUFFNER: We don't have any specific data on either of those.

DR. FARBER: If you want to put up slide 7, this indicates, "Stop and ask a doctor if you have symptoms of a heart attack or stroke." Do you really mean that you want a patient stopping their medication, calling the doctor in a day or two if they have those kinds of symptoms?

DR. KUFFNER: So this language is class NSAID labeling that was provided by FDA across all NSAIDs. I agree with you. I think, at the end of the day, they do need to stop use and, certainly, if they have these symptoms, seek emergency medical care.

DR. FARBER: Yes, absolutely.

DR. NEILL: Dr. Cunningham?

DR. CUNNINGHAM: Yes, my question is on the 1,300 ibuprofen users. Just wondering where you got those users and did you have a sense of their health literacy? Because I come from an area where health literacy and literacy in general is incredibly low.

DR. KUFFNER: Sure, I think Dr. Schiffman maybe will answer that question for you.

DR. SHIFFMAN: Sure. First, let me introduce myself. I'm Saul Shiffman. I'm a health psychologist and a professor at the University of Pittsburgh in psychology and pharmaceutical sciences. Together with Dr. David Kaufman from BU, I was the principal investigator on this study and I do consult to Johnson and Johnson on consumer behavior in OTC products.

So these data were collected from online research panels. And we did not have a measure of health literacy. We do know their education and approximately, call it, 20 percent had not gone beyond high school. And what we see is that their

rate, for example, of exceeding the daily OTC limit is about the same as those who have gone onto college and beyond.

But because it was online and because of other things we were doing, we don't have a health literacy measure.

DR. CUNNINGHAM: So I'd be happy if only 20 percent of my patients hadn't gone on beyond high school. So I think it really is a limited patient population and I worry about other patient populations.

DR. SHIFFMAN: No, I agree with you that the very lowest end of education and people with very limited health literacy are underrepresented, but we don't see a trend toward more frequently going over the limit as we look at an educational gradient, but indeed it's not fully representative of particularly the low end of education of literacy.

DR. NEILL: Dr. Chung?

DR. CHUNG: James Chung, Amgen. So I have two questions related to the FDA presentation a

little earlier. One is about the baseline characteristics of the RA patients. And I don't know whether there were data collected that would give you some indication about the level of disease activity or severity of patients among the three groups and, if so, if it gave you a sense of balance there.

Then the other was, it was noted that the DMARD use was balanced among the three groups and some detail about whether you looked at, for instance, the percentage of biologics used, corticosteroid use across the three groups, whether percentage or dose.

DR. POKROVNICHKA: Yes.

DR. NEILL: Just state your name.

DR. POKROVNICHKA: This is Dr. Pokrovnichka, FDA. Unfortunately, there weren't any data to help us understand what was the severity of the underlying disease for both OA and RA patients in this study. All we know is that the baseline score on visual analog scale was 52, 53, which falls into the category of moderate pain.

However, we don't know if this baseline score was collected while patients were taking pain medication, any type of pain medication, or not. We don't know if these patients were responders or non-responders to non-steroidal or if they were on concomitant opioids, duloxetine, intermittent, intraarticular injections of hyaluronic acid or steroids, physical therapy, x-ray images, grading of their osteoarthritis. We don't have this data.

It was interesting when we saw that, especially in the rheumatoid arthritis population, but keeping in mind these were a limited number of patients because it was only 10 percent of the study population. Naproxen was labeled as the drug, based on the data we looked at, having more deaths.

It was interesting when we looked at the reasons for why these patients were dying. It was primarily due to infections and malignancies. DMARD use is connected. It's the leading cause of RA patients dying from infections and malignancies.

Then we attempted to look further.

Unfortunately, these are all post-randomization analyses and based on very, very small numbers of patients, only 45 patients, if I recall from naproxen, from all groups.

The use of DMARD was imbalanced only between patients who died. Okay? But it was balanced at randomization and during the study. So you can't really explain. It's interesting, but there are limitations that we cannot give you the answer.

DR. NEILL: Thank you. Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau, two questions, one I guess to FDA or Pfizer. Is there any reason that we would expect differential effects by any of the baseline characteristics like age, or sex, or race? Was that discussed? I realize that it could be a small-number issue to look at, but I'm just wondering if there's an expectation that there might be different effects by any of those characteristics.

DR. HERTZ: This is Sharon Hertz. Are you asking, for instance, different effects regarding the cardiovascular or other outcomes?

DR. BOUDREAU: The cardiovascular.

DR. HERTZ: If the baseline characteristics were imbalanced, we know that older patients can have worse renal function. We know that there may be greater degrees of cardiovascular disease. They may be more prone to gastrointestinal bleeding from the platelet inhibition.

So age can be a factor that's associated with some of the risks with NSAIDs. For some of the other characteristics, I can't think of any based on race or gender specific for this class of drug, but there may be some who know otherwise, but that certainly hasn't come up. Is that what you were asking?

DR. BOUDREAU: Yes, yes, no, thank you. My second question is a bit different. Do we know the proportion of ibuprofen users and naproxen users that is prescription use versus OTC use? And I ask that question, the message that will come out from this trial; it happens that sometimes the specifics around the comparator of dose and indication get lost. And so I'm curious what the market segment

is of prescription versus OTC if we know.

DR. HERTZ: So my understanding is there were a very small percent of patients who might have been on less than the prescription dose.

DR. RACOOSIN: This is Judy Racoosin. You mean overall in the market? Is that what you're getting at?

DR. BOUDREAU: Overall in the market, yes.

DR. RACOOSIN: So if you go to slide 3, my slide 3, this is just very relative. Okay? So you can see this in 2017. There were 45 million prescriptions dispensed for ibuprofen and 18 million for naproxen. Okay? So those are prescriptions dispensed from retail pharmacies.

Then if you go to slide 5, these are the numbers of packages sold per year. Okay? So 173 million ibuprofen compared to 45 million prescriptions dispensed, so you can't make exactly a direct comparison, but just to give you sort of relative terms of numbers of packages sold from OTC versus -- but there's also patients who get a prescription for an NSAID that is also available

OTC.

There are probably a lot of different factors that go into who gets a prescription for a product that's available OTC that need to be taken into account. Thank you.

DR. NEILL: Dr. Kuffner, did you want to speak to that?

DR. KUFFNER: Yes, Dr. Kuffner. We know from the Consumer Behavior Surveillance Study that 87 percent of the users -- and again, these were ibuprofen users. That's how you had to get into this study. But 87 percent of users used OTC ibuprofen only.

DR. NEILL: Thank you. Dr. Schmid?

DR. SCHMID: Yes. This, I think, is a pretty minor question, but on slide 27 and 28 of the FDA where this was the one that Ms. Robotti was talking about earlier with deaths by trial period, slide 27 has a line labeled deaths, CRF dataset, and slide 28 has a slide labeled deaths.

Also in the FDA briefing document, table 9 has an all-cause deaths and I'm getting different

numbers in all those tables. And my question was just, should they all be the same? Or is this, like, a typo or is there slight differences in one of those tables?

DR. HERTZ: This is one of the challenges we have with study reports. I don't know why we get study reports that have different numbers for deaths. So it seems to me that investigators should be instructed how to report deaths in a manner that's consistent and clear, but when we were going through this review, we found all kinds of different numbers.

So I think the question of why this happens really has to go back to Pfizer, and the protocol, and how was it that deaths that occurred were not captured in different datasets. All we can do is go through the data and try and piece things together based on what we get.

DR. NEILL: Dr. Rosenberg?

DR. ROSENBERG: Thank you, Rosenberg. This was more a comment regarding the Johnson and Johnson survey, which is very good and useful

information. But my comment was just to caution about the use of real-world data. As I think Dr. [indiscernible] had mentioned, we see a proportion of patients having higher than high school education.

These data are no more representative of real world than the clinical trial dataset is at answering an online health survey and its self-selection bias. So I think they should be viewed in this context.

DR. NEILL: Dr. Ohman?

DR. OHMAN: Magnus Ohman. This is for Dr. Kuffner. So as best as I can tell, ibuprofen is the market leader for the use of OTC therapy. You went through your presentation and I didn't see any data on safety. And maybe it was because I wasn't here in 2005. This was a long time ago. But I would have expected that the market leader would provide some information that I as a practicing physician can actually hang my hat on on the safety or cardiovascular safety of a therapy.

DR. KUFFNER: So we didn't put it in the

presentation. This is Ed Kuffner. We did put it in the briefing book. There are a number of different meta-analyses that have looked at it. The Bally meta-analysis was one of the more recent ones. It was done between 2014 and today. And in that meta-analysis, when you broke out with the doses between OTC type of doses compared to prescription doses, they did see a lower risk for the OTC doses compared to the prescription doses.

DR. OHMAN: But it is higher than placebo. Right?

DR. KUFFNER: Those studies looked at -- I think it was compared to non-users, so they didn't compare it to placebo with those meta-analyses.

DR. NEILL: Dr. Parker?

DR. PARKER: So this is a bit of a follow-up to a question that was asked earlier about monitoring of medication adherence during PRECISION and, knowing what the people enrolled in the different arms were actually taking. And I know there were not MEMS caps. I got that. And they weren't electronic tracking mechanisms to know

exactly, or blood levels, or whatever.

But I would think that there was definitely some tracking to know what medications people actually were taking in pill count. And so this gets down inside of that. My question is, within PRECISION, what can you tell us about the enrollees and the excess dose of ibuprofen or Naprosyn that people were taking given the availability of having been prescribed, maybe still having pain, maybe having been given up to the maximum recommended dose and then still being in pain and having availability over the counter as we heard from your colleague, I mean, over 900 products available that have these different medications and an ability to sort of understand that and navigate that as a patient or consumer who is enrolled in PRECISION.

So let me state the question again. How many super-utilizers of ibuprofen and Naprosyn were there in PRECISION and what can you tell me about them?

DR. PRESSLER: I'm assuming you're directing that to Pfizer, so Milton Pressler, Pfizer. So in

the interim, we huddled and got some information to the question that you have. So during the follow-up visits, the coordinator would look at the blister packs coming back and evaluate whether the patient was compliant within 80 to 120 percent of the dispensed dose.

They recorded that on a case report form. Okay? So that was the way we were tracking the medication. Then in terms of super users, I think Dr. Nissen showed that some of the patients that were still in pain took other NSAIDs and that amounted to about 8 or 9 percent of the patients.

What dose they ended up on, I'm not sure that I can tell you, but it's not that that was unbalanced between the groups. So each of the randomized treatment groups, whether they randomize to celecoxib, ibuprofen, or naproxen, the number of patients who took additional NSAIDs was approximately the same and amounted to about 90 percent.

DR. PARKER: Do you know high and how adverse the outcomes related were to those that

were super users? Like, what happened?

DR. NISSEN: Can you go back to 185, please, slide SA-185? I want to answer directly the question you asked, which I think is an important one. So I will show you this. So there are cross the three treatment arms use of non-randomized celecoxib, non-randomized ibuprofen, and non-randomized naproxen, no small numbers.

Then there are other NSAIDs that come into play. The important, I think, take-home here is that this drop-in to non-study medications was balanced across the three treatment groups. It's a very important and very good question, so thank you.

Now, with regard to outcomes in those patients, we don't have an analysis of that. And I think it'd probably be very hard because, if you look at the percent of the patients in the trial that dropped in, it's very small, so the dataset's going to be very sparse.

Adjournment

DR. NEILL: Thank you all. We've come to

the end of a very long and complex day that a lot of people have done a lot of work on over the years. Thank you to industry and for those of you on the committee.

The meeting for today is now adjourned. Panel members, please remember that there should be no discussion of the meeting topic amongst yourselves or with any members of the audience.

Please take all of your personal belongings with you as the room is being cleaned at the end of the meeting day. All materials that are left on the table will be disposed of. You can leave your nametag. Take everything else. We will reconvene tomorrow at 8:00 a.m. Please bring your materials back with you tomorrow morning. Place card, nametag; take everything else. Take that, too.

(Whereupon, at 4:50 p.m., the meeting was adjourned.)