UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

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January 24, 2018
8:30 a.m.

FDA White Oak Conference Center
Building 31, Room 1503
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Silver Spring, MD 20993

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M E E T I N G

(8:30 a.m.)

DR. HUANG: All right, good morning. We'll go ahead and get started. I'm Phil Huang, the Chair of the Tobacco Products Scientific Advisory Committee. And good morning to everyone, and thank you for joining us. I want to make a few statements and then we will introduce the Committee.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. 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 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. Thank you.

MS. COHEN: The Center for Tobacco Products of the Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972 and the Family Smoking Prevention and Tobacco Control Act of 2009.

The Committee is composed of scientists, healthcare professionals, a representative of the state government, a representative of the general public, *ex officio* participants from other agencies, and three industry representatives.

With the exception of the industry representatives, all Committee members 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 this Committee's compliance with applicable federal conflict of interest law and regulations is being provided to participants in today's meeting and to the public.

The purpose of today's meeting is to discuss modified risk tobacco product applications submitted by Philip Morris S.A.

for the IQOS system with Marlboro HeatSticks, IQOS system with Marlboro Smooth Menthol HeatSticks, and IQOS systems with Marlboro Fresh Menthol HeatSticks. Accordingly, this meeting is categorized as one involving a particular matter involving specific parties.

Based on the categorization of this meeting and the matters to be considered by the Committee, all meeting participants, with the exception of the three industry representatives, have been screened for potential conflicts of interest. FDA has determined that the screened participants are in compliance with applicable federal conflict of interest laws and regulations.

With respect to the Committee's industry representatives, we would like to disclose that Drs. William Andy Bailey, Willie McKinney, and David Johnson are participating in this meeting as non-voting representatives. Dr. Bailey is acting on behalf of the interests of the tobacco growers. Dr. McKinney is acting on behalf of the interests of the tobacco manufacturing industry. And Dr. Johnson is acting on behalf of the interests of the small business tobacco manufacturing industry. Their role at this meeting is to represent these industries in general and not any particular company. Dr. Bailey is employed

by the University of Kentucky. Dr. McKinney is employed by Altria Client Services. And Dr. Johnson is employed by National Tobacco Company.

We ask that you please do not approach the head of the table at any time before the meeting, during breaks, and during lunch or after the meeting.

There's no use of flash photography or TV camera lights while the meeting is in session.

And our press contact is Michael Felberbaum, and he is in the audience in the back there.

And I'll also ask that you please turn off your cell phones, if possible. Thank you.

DR. HUANG: Okay, we will now go through introduction of the Committee members. And again, I'm Phil Huang with the Austin Public Health Department.

DR. GIOVINO: Hi, my name is Gary Giovino. I'm with the University of Buffalo School of Public Health and Health Professions.

DR. MERMELSTEIN: I'm Robin Mermelstein. I'm with the Institute for Health Research and Policy at the University of Illinois at Chicago.

DR. BIERUT: I'm Laura Bierut. I am a physician at

Washington University in St. Louis.

DR. O'CONNOR: Richard O'Connor with the Roswell Park Comprehensive Cancer Center.

DR. WANKE: Kay Wanke with the National Institutes of Health, the Office of Disease Prevention.

DR. KING: I'm Brian King with the U.S. Centers for Disease Control and Prevention.

DR. McLOUGHLIN: I'm Kris McLoughlin, SAMHSA, Substance Abuse and Mental Health Services Administration.

DR. JOHNSON: I'm David Johnson. I'm with National Tobacco, and I'm representing the interests of the small tobacco manufacturers.

DR. BAILEY: Andy Bailey, University of Kentucky, dark tobacco extension specialist, representing tobacco growers.

DR. McKINNEY: My name is Willie McKinney, and I serve as the Industry Representative of TPSAC. I'm also employed by Altria Client Services as Vice President of Regulatory Affairs. And in full disclosure, I should say that through agreements with Philip Morris International, Philip Morris USA will have exclusive rights to commercialize the IQOS system in the United States if authorized by FDA. And PM USA and ALCS collaborated with PMI on the modified risk tobacco application and related

presentations that are the subject of this meeting.

DR. FAGAN: Good morning. My name is Pebbles Fagan. I'm with the College of Public Health at the University of Arkansas for Medical Sciences.

DR. WEITZMAN: My name is Michael Weitzman. I'm a pediatrician at New York University School of Medicine and the College of Global Public Health at NYU.

DR. THRASHER: Hi, good morning. Jim Thrasher from the Arnold School of Public Health, the University of South Carolina.

DR. REES: Good morning. Vaughan Rees, Harvard School of Public Health, Department of Social and Behavioral Sciences.

DR. BLOUNT: I'm Ben Blount from the U.S. Centers for Disease Control and Prevention.

DR. APELBERG: Good morning. I'm Ben Apelberg. I am the Director of the Division of Population Health Science in CTP's Office of Science.

DR. HOLMAN: Good morning. I'm Matt Holman. I am the Director for the Office of Science here at CTP.

MR. ZELLER: Good morning. Mitch Zeller, Director of the Center for Tobacco Products, FDA.

DR. HUANG: Okay. Welcome, everyone. And I think, next

on our agenda is Mitch Zeller.

MR. ZELLER: On behalf of the Food and Drug Administration and the Center for Tobacco Products, I want to welcome everyone here in the room with us today as well as everyone viewing the live webcast. A great turnout in the room, by the way. Thank you all for coming in person. Thank you for joining us for the meeting of FDA's Tobacco Products Scientific Advisory Committee.

Last July, FDA announced the comprehensive plan for tobacco and nicotine regulation. Despite progress in tobacco control and prevention, tobacco use remains the leading cause of preventable disease and death in the United States.

Combustible cigarettes cause the overwhelming majority of tobacco-related disease and are responsible for more than 480,000 deaths in the United States each year. That is why a key piece of FDA's new approach is demonstrating a greater awareness that nicotine in cigarettes, while highly addictive, is not directly responsible for all of the diseases, from the cancer to the lung disease to the heart disease, that's attributed to smoking.

Nicotine is delivered through a variety of products that represent a continuum of risk. These products include

everything from cigarettes to FDA-approved smoking cessation aids, like the nicotine gum, patch, and lozenge.

FDA's comprehensive plan for tobacco and nicotine regulation has two primary parts: first, exploring the reduction of the addictiveness of combustible cigarettes; and second, recognizing and clarifying the role the potentially less harmful tobacco products could play in improving public health. Modified risk tobacco products, or MRTPs, in general, are an important component of this plan.

Today and tomorrow, TPSAC will hear evidence and participate in an in-depth discussion about three modified risk tobacco product applications submitted by Philip Morris Products S.A.

FDA has an incredibly important responsibility when reviewing tobacco products seeking authorization to be sold or distributed for use to reduce the harm or the risk of tobacco-related disease.

The Tobacco Control Act outlines the requirements that must be met before FDA can authorize the marketing of an MRTP. We must ensure that modified risk claims are substantiated and supported by scientific evidence. It is our legal and ethical obligation to make sure the public is not misled about the

relative risks of a tobacco product. Nor should consumers be faced with claims for products that are confusing or unclear.

Applicants must demonstrate that a proposed MRTP product, as actually used by consumers, will significantly reduce risks to individual users of the product and benefit the population as a whole. We must take into account both tobacco users and nonusers in the evaluation of MRTP applications.

When evaluating the prospective impact of marketing a tobacco product as modified risk, FDA must consider the likelihood that users who would have otherwise quit tobacco completely may instead switch to the modified risk product or use the modified risk product along with traditional tobacco products. We must also consider the likelihood that nonusers of tobacco will initiate tobacco use with the modified risk product, possibly leading to the use of potentially more dangerous products.

I want to remind everyone that FDA's role in evaluating MRTP applications is not to determine whether the product itself meets the requirements for being marketed or for staying on the market. That is called the premarket authorization process, and it is separate from the MRTP review. Rather, MRTP is about whether the product may be sold for use to reduce the

harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.

The MRTP application review process has unique opportunities for public participation. Unlike other types of applications accepted for review by FDA, such as new drug applications, MRTP applications themselves are made available to the public on our website. Additionally, we open a docket for every MRTP application accepted for review in order to solicit comments and scientific data from the public.

All MRTP applications are then discussed in the open public forum of a TPSAC meeting, like the one we are holding today and tomorrow. And tomorrow, members of the public will have the opportunity to present their comments to the Committee.

So, TPSAC members, you have your work cut out for you over these 2 days, but I'm confident that you will carefully consider the scientific evidence that has been provided to you in the briefing materials, and that will be presented today by the Applicant and by FDA's own scientists.

Your task is to provide FDA with your assessment and recommendations on the matters brought before you for discussion. We thank you in advance for being part of this

important process.

Before I close, I'd like to especially thank three members of TPSAC who, when this meeting concludes tomorrow, will have come to the end of their terms on the Committee. I've known each of them for many years and hold them in the highest professional regard.

First, Dr. Pebbles Fagan, Director of the Center for the Study of Tobacco at the Fay W. Boozman College of Public Health at the University of Arkansas for Medical Sciences. Pebbles, your research to prevent tobacco-related disease, along with your dedication to reducing health disparities, is both remarkable and commendable. Your scientific acuity, combined with your keen insights regarding impacts on vulnerable populations, has provided this Committee with a level of awareness that will continue even as you complete your service on TPSAC, and we thank you.

Second, Dr. Richard O'Connor, Professor of Oncology at Roswell Park Cancer Institute. Rich, your research and knowledge of consumer interest and use of novel tobacco products has been an extraordinary help to the Committee. You've set the bar high with the breadth and the depth of your knowledge and expertise in regulatory science, abuse liability,

consumer perceptions, and disease pathology and prevention. Your unique ability to identify and articulate key issues in Committee deliberations has been invaluable, and we thank you for serving on TPSAC.

And finally, and I warned him I would do this, I want to give my most sincere thanks and appreciation to our Committee Chair, Dr. Philip Huang. Dr. Huang is the Medical Director and Health Authority for Austin Public Health. Thank you, Phil, for your dedication to public health, chronic disease prevention, and tobacco control. And thank you for providing strong, insightful, and objective leadership during your term as chairman. You will be sorely missed after today and tomorrow's proceedings. And please accept our deepest congratulations for a job well done.

So to the audience in the room and viewing the webcast, thank you all again for joining us. We have an important 2 days ahead of us. And now I'd like to turn the meeting back to Dr. Huang.

Thank you.

DR. HUANG: Thank you, Mitch.

And next, I think we have an introduction to our meeting topics by Dr. Apelberg.

One thing before we start. I do want to acknowledge Dr. Ossip is participating via phone.

Welcome, Dr. Ossip.

DR. OSSIP: Thank you.

DR. APELBERG: Good morning, everyone. My name is Dr. Benjamin Apelberg, and I'm the Director of the Division of Population Health Science at CTP's Center for -- at the Center for Tobacco Products in the Office of Science. I'm going to present a brief overview of the MRTPA pathway as well as an introduction to the applications that are under review from Philip Morris Products S.A.

First, I'll start with this disclaimer. Just to let you know, this disclaimer is relevant to all FDA presentations. All FDA presenters have this in their slides, but I will be the only one to read it.

The information in these materials is not a formal dissemination of information by FDA and does not represent Agency position or policy. The information is being provided to TPSAC to aid in its evaluation of the issues and questions referred to the Committee.

This presentation contains information prepared by the FDA for the members of the TPSAC. The presentation describes

assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

This presentation may not include all issues relevant to FDA's decision on the applications and, instead, is intended to focus on issues identified by FDA for discussion by TPSAC. The FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments has been considered and all FDA reviews have been finalized. FDA's determination may be affected by issues not discussed at the TPSAC meeting.

So now, just for a brief outline of what I'll be discussing, I'll first start with a high-level overview of the statutory framework for modified risk tobacco products and the FDA review process. I'll then provide a brief summary of the applications currently under review and, finally, a summary of the questions that we're asking the Committee to answer during this 2-day meeting.

Section 911 of the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control

Act, defines a modified risk tobacco product as a tobacco product sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.

This includes products whose label, labeling, or advertising represents, either implicitly or explicitly, that the product is less harmful or presents a lower risk of tobacco-related disease than other commercially marketed tobacco products, or that the product or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain or is free of a substance. This also includes products which use the descriptor of "light," "mild," or "low" or similar descriptors.

In a moment I'll talk about the standards for modified risk tobacco products as laid out in the statute, but I first want to provide a little more context for the MRTP pathway.

Before an MRTP can be marketed in the United States, an order from FDA under Section 911(g) of the Federal Food, Drug, and Cosmetic Act must be in effect with respect to the tobacco product.

To legally sell an MRTP that is also a new tobacco product, a company must have authorization from FDA under both

Section 911, in other words, an MRTP order, and Section 910, substantial equivalence order, premarket tobacco product order, and/or exemption from substantial equivalence.

I did want to let everyone know that Philip Morris Products S.A. has stated that it submitted a premarket tobacco product application for the IQOS system and HeatSticks to the FDA. This meeting, however, is focused on the modified risk tobacco product applications.

Under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act, in determining whether a modified risk order should be issued, FDA must assess whether it has been demonstrated that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. We call this a risk modification order.

Alternatively, for products that cannot receive an order under 911(g)(1), FDA may issue an order under 911(g)(2), which we call an exposure modification order, if

- it determines that the applicant has demonstrated that, among other things, the order would be appropriate to

promote the public health;

- the label, labeling, and advertising is limited to a claim that the product does not contain or is free of a substance or contains a reduced level of a substance or presents a reduced exposure to a substance;

- that the scientific evidence is not available and cannot be made available without conducting long-term epidemiological studies for an application to meet the standards laid out in 911(g)(1), so in other words on the previous slide; and

- the scientific evidence that is available demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies; and

- that testing shows that consumers will not be misled into believing that the product has been demonstrated to be less harmful or to present less risk.

The evaluation of an MRTPA can be thought of in terms of a few key overarching questions. So, first, CTP has to consider is there adequate scientific substantiation of the proposed modified risk information?

The second question addresses the health risks of the

product, so what are the relevant health risks of the MRTP to individual tobacco users?

Third: How do consumers perceive, understand, and comprehend the modified risk information? And how do their perceptions, understanding, and comprehension affect or impact potential benefits and harms?

And then what are the potential benefits and harms to the health of the population as a whole that will be associated with an MRTP marketing order?

This figure presents a summary of the MRTPA review process. Often, applicants will request a meeting with the Agency to discuss their potential application. That's described as Phase 0 here.

When FDA receives an application, an acceptance review is conducted to ensure that it meets certain basic requirements, such as being legible and in English.

The next step is the filing review to ensure that the application includes the required information as described in the statute.

Once filed, the application undergoes substantive scientific review, and in the case of MRTPA is a referral to the TPSAC as well as the posting of the applications for public

comment.

After complete review, FDA will issue a decision. If an order is granted, the applicant would conduct agreed-upon postmarket surveillance and studies. MRTP orders are time limited; therefore, a renewal would be needed to continue marketing a product as modified risk.

So now to the applications under review and the focus of this TPSAC meeting:

On December 5th, 2016, FDA received applications from Philip Morris Products S.A., PMP S.A., which states that the Applicant is requesting MRTP orders under Sections 911(g)(1) and 911(g)(2) for the IQOS system with Marlboro HeatSticks, the IQOS system with Marlboro Smooth Menthol HeatSticks, and the IQOS system with Marlboro Fresh Menthol HeatSticks.

On May 24th, 2017, FDA filed the applications and began substantive scientific review.

The Applicant describes the IQOS tobacco heating system as a heat-not-burn tobacco product consisting of a HeatStick, which is described as a filtered non-combusted cigarette containing a tobacco plug, designed to function with the IQOS holder and to produce an aerosol when the plug is heated; the holder, in which the HeatStick is inserted, which heats the

tobacco material by means of an electronically controlled heating blade; and the charger, which is used to recharge the holder after each use.

The Applicant requests modified risk orders to market these products as follows. One set of labeling and advertising includes the following statements:

- The IQOS system heats tobacco but does not burn it.
- It significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risk of tobacco-related diseases.

A second set of labeling and advertising includes the following statement:

- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

And finally, a third set of labeling and advertising includes the following statements:

- The IQOS heats tobacco but does not burn it.
- It significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching

completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

This last set of labeling and advertising corresponds to the requests under 911(g)(2).

The Applicant, in their submission, acknowledges that the statutorily mandated cigarette warnings are applicable to the products that are the subject of these applications, given their regulatory classification as cigarettes. However, the Applicant has developed and tested alternative statements intended to improve comprehension and understanding, described in the applications as PMI Important Warnings.

One example is listed on this slide. It says Important Warning:

- Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.

- HeatSticks contain nicotine, which is addictive.

- And using the IQOS system can harm your health.

The applications submitted to and filed by the FDA include a range of scientific investigations, including the scientific studies listed here, many of which will be discussed in the

subsequent presentations.

So now I'd like to spend a few minutes talking about the questions that we have brought to the Committee. I'll go over them now so that the Committee can think about these issues as they are listening to the presentations from the Applicant and from FDA reviewers.

The first question for the Committee is as follows:

1. Discuss evidence related to the health risks of the IQOS system and the appropriateness of the proposed modified risk information.

a. Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true:

"Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases."?

And this is a voting question.

b. Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true:

"Switching completely to IQOS presents less risk

of harm than continuing to smoke cigarettes."? This is also a voting question.

2. Discuss evidence related to human exposure to harmful or potentially harmful chemicals when combusted cigarette smokers completely switch to the IQOS system, including the implications of changes in exposure for long-term disease risk and the appropriateness of the proposed modified risk information.

a. Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true: "Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."? This is a voting question.

b. If the answer to question 2a is "yes," has the applicant demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality?

This is a voting question to be answered by Committee members who voted "yes" to 2a.

3. Discuss evidence regarding the likelihood that existing combusted cigarette smokers will initiate use of the IQOS system, completely switch to IQOS, and/or become long-term dual users of IQOS and combusted cigarettes.

a. What is the likelihood that that U.S. smokers would completely switch to use of the IQOS system?

This is a voting question with the options high, medium, or low.

b. What is the likelihood that U.S. smokers would become long-term dual users of IQOS and combusted cigarettes?

And the options here, once again, are high, medium, or low.

4. Discuss evidence regarding the likelihood that persons who do not use tobacco products will start using the IQOS system.

a. What is the likelihood that U.S. never smokers, particularly youth, will become

established users of the IQOS system?

The options are high, medium, or low.

b. What is the likelihood that former smokers will re-initiate tobacco use with the IQOS system?

The options are high, medium, or low.

5. Discuss evidence regarding consumer comprehension and perceptions of the proposed modified risk labeling and advertising.

a. Has the applicant demonstrated that, after viewing the proposed modified risk labeling and advertising, consumers accurately understand the risks of IQOS use as conveyed in the modified risk information?

And that's a voting question.

And then 5b has changed slightly from what was -- what's in your packet, but this is the updated question here.

b. What additional information, if any, needs to be communicated, other than what has been proposed by the applicant, for consumers to understand the health risks of the IQOS system?

So those are the questions that we've brought to the

Committee for this 2-day meeting. I'll now stop, and I can take clarifying questions if anyone has any.

DR. HUANG: Any questions for Dr. Apelberg?

DR. APELBERG: Oh, I think there's one.

DR. HUANG: Yes, Dr. Weitzman.

DR. WEITZMAN: If you look at the slide "Modified Risk Tobacco Products Defined," it says that "the product" -- the last bullet, "The product or its smoke contains a reduced level of." And then I won't read the rest. But if we're talking about something that produces vape or vapor or an aerosol, is smoke the appropriate term? Is that what we're really looking for?

DR. APELBERG: This is language pulled from the statute that just describes -- they're not all things that have to be met for something to be a modified risk tobacco product. It essentially is describing -- that statement basically, if a product or its smoke, you know, if it's communicated on the labeling that a product or its smoke contains reduced level of exposure, you know, lower levels of chemicals and so forth, and that would be -- that would be part of what would be defined as a modified risk tobacco product. So it doesn't mean that there has to be -- you have to be talking about the smoke. That's

just a broad, all-encompassing set of statements.

DR. WEITZMAN: Thank you.

DR. HUANG: Any other questions?

(No response.)

DR. HUANG: Okay.

Well, thank you, Dr. Apelberg.

Now, you see on our agenda there's a break scheduled for now, but we're a little ahead of schedule, so we're thinking we'll keep pushing along and maybe take a break after, perhaps, two of the Philip Morris presentations. So if we can go ahead and proceed with the next agenda item, the IQOS system and heating technology presentation by Dr. Gilchrist.

DR. GILCHRIST: Good morning. I'm Moira Gilchrist from Philip Morris International. Thank you, Mr. Chairman, members of the Committee, members of FDA, and everyone here today. We're here to present our modified risk tobacco product application for IQOS.

Mr. Chairman, we have an integrated 90-minute presentation with four different speakers, and we'd appreciate the opportunity to deliver the full presentation, after which we'd be very happy to answer any questions that the Committee may have.

To begin with, I'll take a few moments to consider the application from the perspective of the 40 million American men and women who currently smoke.

For smokers, cigarettes are familiar. They're the most widely used tobacco product in the United States. I'm sure that most people in the room know someone who smokes. It could be a friend, a colleague, or a family member. Smokers live in every region of the United States. They're represented in every ethnicity, every religion, and every socioeconomic group. Their best choice would be to quit altogether, but the fact is that most don't. This is the status quo.

To help our discussion, we've illustrated the situation with a very simple diagram. This represents the approximately 40 million Americans who currently smoke. Of course, the picture doesn't remain static. Every year there's a group of people who start smoking. At the same time, there are a number of smokers who quit, but some of them relapse and return to smoking. There are varying estimates of the rates of each flow in the future. But the key point is that World Health Organization and U.S. government statistics predict that tens of millions of American men and women will continue to smoke.

This is the situation that the U.S. government has been

seeking to address for decades, most significantly in 2009 with the Family Smoking Prevention and Tobacco Control Act. The statute aims to deliver real-world solutions to a decades-old problem. It empowers the FDA to change the status quo for 40 million Americans.

As part of the solution, the statute and the FDA recognize the continuum of risk for nicotine and tobacco products. On this continuum, combustible products are, by far, the most risky because it's the burning of tobacco that creates the vast majority of the harmful chemicals contained in cigarette smoke that are the primary cause of smoking-related disease.

Cessation, of course, is the best way for a smoker to lower their risk. But we know that many don't. We also know from PATH data that more than half of those who continue to smoke are seeking lower-risk alternatives. And the statute mandates that FDA oversee industry's efforts to develop and introduce modified risk products to help move smokers away from cigarettes.

Under the statute, we're seeking authorization of IQOS as a modified risk tobacco product. IQOS heats tobacco rather than burning it. Because of this, it generates an aerosol that contains, on average, greater than 90% lower levels of harmful

and potentially harmful chemicals compared with cigarette smoke.

Through the course of the presentation, we'll show you how IQOS can help change the status quo for millions of American smokers and lead to significant reductions in harm and the risk of tobacco-related disease.

To be clear, IQOS is not a perfect solution. It's not risk free, and it contains nicotine, which is addictive. The best choice for a smoker is to quit altogether. But for those who don't, our evidence shows that IQOS is a much better choice than continuing to smoke.

As you see, we've added IQOS to this slide. Our data show that it can move millions of those, who would otherwise continue smoking, away from cigarettes without materially impacting initiation or cessation. It's a real-world solution.

I used to be a smoker. I'm a scientist, and I work every day on issues related to the health effects of smoking, and yet I continued to smoke. Several years ago I switched completely to IQOS. I find it an acceptable alternative to smoking, and I also knew the reasons to switch. I knew the science that you're going to hear about today.

For American men and women who smoke, your friend, your

colleague, or your family member, shouldn't they have access to and information about a product that's a better choice than smoking?

The statute gives FDA the authority to change the status quo by verifying that products which claim to reduce harm and risk actually do, and by making those products available and ensuring that smokers are accurately informed about them.

Beginning with Part A, the science in our application is a comprehensive package of both clinical and nonclinical data. Our data demonstrate that smokers who switch completely to IQOS are exposed to much lower levels of toxicants. As you'll see shortly, the ultimate result of this is significantly reduced harm and the risk of tobacco-related diseases.

Part B of the statute requires modified risk tobacco products to benefit the health of the population overall. This requires us to assess intended use by smokers who would otherwise continue to use cigarettes, and unintended use by nonsmokers and smokers who would otherwise stop.

So the question is does the likelihood and magnitude of intended use outweigh the likelihood and magnitude of unintended use? Well, we'll show you why there's a high probability that the answer to this question is yes.

Our premarket data from the United States indicate that when given accurate product information, millions of American men and women who would otherwise continue to use cigarettes could switch completely to a much better product. This is in line with our real-world experience in more than 30 countries where the product is already available.

More than 3.7 million smokers outside the U.S. have switched exclusively to IQOS in only 2 years. At the same time, nonsmokers and former smokers show very little interest in the product.

Our application includes three product messages that clearly communicate the results of our scientific assessment.

Message 1: Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.

Message 2: Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

And Message 3: Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.

These messages would appear along with the Surgeon General's warnings.

I acknowledge that many in the public health community are

skeptical about our motives. The controversial history of the industry is laid out vividly in the statute. But at the same time, the statute created this process and provides for effective oversight of our efforts to develop and introduce less harmful products. And that's exactly why we're here today. We appreciate your expert evaluation of our science based on the strength of our application and the opportunity that it presents to America's smokers. If you decide that using IQOS would be a better choice than continuing to smoke, then U.S. smokers need to have access to it and information about it. You may ultimately find that we can help change the status quo in a rapid and unprecedented way.

Let's turn to our agenda. First off, I'll take a few minutes to show you the IQOS system and heating technology.

Then Manuel Peitsch, who is our Chief Scientific Officer, will outline the core of our scientific assessment results.

After that, we'll look at benefit to the population as a whole. Antonio Ramazzotti, who is our Vice President of Human Insights and Behavioral Research, will share our perception and behavior data.

Philip Morris USA, our former sister company, will sell IQOS in the United States if authorized by FDA. Sarah

Knakmuhs, who is their Vice President of Heated Tobacco Products, will set out our plans for the introduction of IQOS in the United States, including controls to minimize unintended use, as well as plans for postmarket surveillance.

At the end, I'll return to talk about population health impact modeling and I'll conclude our presentation.

Now, let's take a closer look at the IQOS system and its underlying heating technology. We've been working on the IQOS concept for more than a decade. It's very different from cigarettes and consists of three major elements.

First are the HeatSticks. These are designed for use only with IQOS. For the tobacco plug, we use a specific blend of tobacco leaves. They're carefully processed to create a uniform mixture that's formed into a sheet and then crimped. The entire process is designed to produce the highest possible homogeneity of the tobacco. This, in turn, ensures that the aerosol is uniform and consistent, puff to puff and stick to stick.

The second important element is the IQOS holder. It contains a heating blade that heats the tobacco plug from the inside. The blade has a platinum-based heating track that's coated with a thin film of glass. The heating blade is

connected to a printed circuit board that holds the firmware for temperature control. When it's in use, the average temperature across the blade is no more than 350 degrees Celsius. That's 662 degrees in Fahrenheit. A cigarette, on the other hand, burns at about 1,200 degrees Fahrenheit.

The heating blade is also a sensor that continually monitors tobacco temperature. The energy supply is automatically cut off if it detects temperatures above the set limit. Every single heating blade is individually calibrated to ensure precision and reliability over and over again during the course of the product's life cycle.

We use infrared cameras to measure the average blade temperature at different set points. Those temperatures are correlated to specific electrical parameters which are unique to each blade and are stored in the permanent memory of the device. Based on these parameters, the device software precisely regulates the energy supplied to the heating blade to achieve the desired temperature profile.

This slide shows the tobacco temperature at different distances from the surface of the heating blade. As you can see from the uppermost line, the heating blade reaches 350 degrees Celsius, but the lines below show that even the tobacco

that's closest to the blade never gets to this temperature. In fact, most of the tobacco remains below 250 degrees, well below the temperature required for combustion processes to begin, which is 400.

With combustible cigarettes, each puff introduces oxygen into the system and dramatically increases the tobacco temperature. In contrast with IQOS, puffing actually decreases tobacco temperature because fresh air cools the system. You can see this on the graph from the small dips in temperature that appear. This is just one of the many pieces of evidence demonstrating that combustion doesn't occur in IQOS.

The third element is the IQOS charger. It's used to recharge the holder after each use. Both the holder and the charger are manufactured by suppliers who specialize in electronics for medical devices, life sciences equipment, and consumer goods.

Let me explain how the product operates. First, the user removes the holder from the IQOS charger and inserts a HeatStick into the holder and then presses and holds the button. The heating profile begins with a short preheat phase to bring the tobacco up to the correct operating temperature. It then applies a specific and controlled temperature profile

for the duration of the experience, which is 6 minutes or 14 puffs, after which the device shuts off.

The innovative design and engineering that I've just summarized ensures the quality and consistent performance of the IQOS system. It's this performance that leads to the scientific results in our application that Manuel Peitsch will present after our break.

Mr. Chairman.

DR. HUANG: Thank you.

DR. GILCHRIST: Do you want to take a break now?

DR. HUANG: Let's go on to one more. How about that?

DR. GILCHRIST: Okay. Manuel.

DR. PEITSCH: Thank you, Moira.

And good morning, Mr. Chairman, members of the Committee and members of FDA and everyone here today.

I'm going to show how the evidence we have generated through our scientific assessment program supports Part A of the statutory requirement, that IQOS, as it is actually used by consumers, significantly reduces harm and the risk of tobacco-related disease to individual users. Implied in this is the fact that the product should significantly reduce the body's exposure to harmful and potentially harmful chemicals, or

toxicants, for short.

Taken together, these objectives represent the three proposed messages in our application.

The application is extensive and covers 17 nonclinical studies and 8 clinical studies. In conducting these studies, we followed international quality standards, such as ISO, GLP, and GCP, and used validated analytical methods.

In line with the roadmap of the National Toxicology Program for the 21st Century, we developed and applied an innovative systems toxicology-based approach to the nonclinical assessment of IQOS, in addition to employing the well-established toxicology testing guidelines described by the OECD.

Over the past decade, we published more than 30 peer-reviewed publications describing our IQOS assessment studies and over 150 publications describing the approaches and methods we used. All completed studies are included in the application and are available for review.

Due to the time constraints today, I will focus on the most important study results that support the proposed claims.

The framework we developed to assess products with a potential to reduce the risk of smoking-related disease is

informed by what is known from epidemiological evidence. Smoking has been proven to cause a number of severe diseases and population harm.

We based our assessment approach on the causal chain of events triggered by exposure to cigarette smoke that ultimately leads to disease. The causal chain of events starts with the burning of tobacco, which leads to the emission of toxicants by cigarettes.

Smoking cigarettes exposes the body to these toxicants. This exposure then leads to changes in the abundance of a large number of the body's molecules. These changes then cause a disruption of many biological mechanisms. This, in turn, causes changes at the cellular and tissue level. And finally, an accumulation of these changes over time leads to the development of disease and, by extension, population harm.

It is also accepted that smoking cessation leads to reduction in the risk of tobacco-related disease. In fact, quitting smoking is the best way to reduce the harm and risk of smoking-related disease.

Consequently, the epidemiology of smoking and smoking cessation confirms the general principle of toxicology, which states that a reduction in toxic emissions leads to a reduction

in exposure, which in turn leads to a reduction in adverse health effects.

To demonstrate that switching to IQOS reduces harm and the risk of smoking-related disease, our assessment program must demonstrate that IQOS emits significantly lower levels of toxicants than cigarettes.

As a direct consequence of this, switching to IQOS should lead to a significant reduction in exposure to toxicants, and this reduction in exposure should lead to a significant reduction in health effects. In fact, the closer these reductions in exposure are to those observed in smokers who quit, the higher the harm and risk reduction potential of IQOS.

At each step of the causal chain of events, we compared the effect of IQOS aerosol with those of cigarette smoke and cessation. The data I am going to present provides the totality of the evidence that demonstrates that switching to IQOS leads to the reduction of harm and risk of smoking-related disease.

Since IQOS was designed to heat and not burn tobacco, the IQOS aerosol has a very different composition than cigarette smoke. Cigarette smoke, here on the left, has a brown color when captured on the filter pad. It contains 50% water and

glycerin, toxicants, and solid carbon-based nanoparticles.

In contrast, the aerosol of IQOS, shown on the right, is visibly different. It essentially contains water and glycerin with significantly reduced levels of toxicants and, importantly, no solid carbon-based nanoparticles.

The solid carbon-based nanoparticles in cigarette smoke are a hallmark of combustion and have been shown to trigger inflammation and demonstrated to cause lung and cardiovascular disease.

As you can see from these electron microscopy images, smoke from a burning cigarette contains many solid particles, on the left image. In fact, one cigarette contains approximately half a trillion solid nanoparticles which corresponds to approximately 0.7 mg a cigarette. In contrast, the aerosol from IQOS, on the right, does not contain such particulate matter.

Our assessment of the IQOS continues with the comparison of the levels of toxicants contained in the IQOS aerosol with those contained in the smoke of 3R4F reference cigarettes from the University of Kentucky. We selected 54 toxicants for quantification using well-established and validated analytical methods. This includes the harmful and potentially harmful

constituents described in the list of Health Canada, the WHO, and FDA-18.

Here we present only 48 because 6 were below the limit of quantification in both IQOS aerosol and cigarette smoke. As depicted in this graph, the IQOS aerosol from the three variants contains, on average, over 92% lower levels of toxicants than cigarette smoke. While most toxicants are reduced by more than 90%, four are reduced by 80 to 90%, and six are reduced by less than 80%.

In addition to the quantification of these toxicants, we conducted an in-depth comparative analysis of the composition of the IQOS aerosol and the 3R4F smoke. To be as thorough as possible, we used a combination of liquid and gas chromatography coupled with high-resolution mass spectrometry. We identified 4,330 constituents in the 3R4F smoke. Of those, 3,580 were absent from the IQOS aerosol. In comparison, only 750 constituents were identified in IQOS aerosol. Of those, 3 were unique to IQOS and 50 more abundant than in cigarette smoke.

We conducted a full toxicological evaluation of these 53 constituents, and from this, 4 constituents were found to be of toxicological concern because they are potential carcinogens.

Our evaluation, based on the published inhalation toxicology literature, indicates that the level of exposure to these compounds through IQOS are below the level of concern.

The toxicants presented earlier are known to cause smoking-related disease and have been categorized according to the diseases they cause. Here we present the average reduction by disease category and see that the carcinogens, cardiovascular, respiratory, as well as reproductive and developmental toxicants, are all reduced on average by more than 90% in the IQOS aerosol.

Nevertheless, it is important to emphasize that toxicants are still present in the IQOS aerosol, and therefore, IQOS is not risk free.

We have demonstrated that IQOS emits significantly lower levels of toxicants than cigarettes. IQOS does not emit solid particles and does not present new hazards. In the causal chain of events linking smoking to disease, a reduction in toxicant emissions leads to reduction in exposure.

Let's now look at the effects of switching to IQOS on exposure.

To assess this, we compared the level of exposure to toxicants in adult smokers who switched completely to IQOS with

the level of exposure in those who continued to smoke.

We conducted four clinical exposure studies, each with 160 smokers. Two were longer-term studies starting with 5 days in confinement followed by an 85-day ambulatory period where the subjects were sent home to use IQOS in a more realistic setting. The 90-day studies were conducted in the U.S. and Japan. Subjects were randomized to either continue smoking, switching to IQOS, or smoking abstinence.

We measured 16 biomarkers of exposure plus nicotine and its metabolites at baseline on Days 1 through 5, and then on Days 30, 60, and 90. We only present 15 because for toluene, the assessment method was not sensitive enough to detect changes in smoking status, even for smoking abstinence.

Let's first look at the nicotine exposure, product satisfaction, and product consumption data from the U.S. study.

Delivering nicotine at comparable levels to the adult smoker's own cigarettes is important for product acceptance. After an initial adaptation period, study participants randomized to the IQOS group achieved comparable levels of nicotine uptake.

Importantly, nicotine exposure did not increase above levels observed at baseline, nor did it exceed the exposure

levels in those who continued to smoke their usual cigarettes.

Satisfaction with IQOS measured with the modified Cigarette Evaluation Questionnaire converges with that of cigarettes after an initial adaptation period. We observed a similar pattern of convergence between IQOS HeatSticks and cigarette consumption over time.

Together, these data demonstrate that smoker acceptance of IQOS is similar to that of cigarettes.

Let's now turn to the data on toxicant exposure. I will show a couple of examples from the U.S. study to demonstrate how the reduction in emission translates to a reduction in exposure before presenting the full exposure profile.

The IQOS aerosol contains 98% less carbon monoxide than cigarette smoke. This leads to a rapid and significant reduction in the levels of carboxyhemoglobin, the biomarker for carbon monoxide, which levels off after only 2 days and is maintained for the full duration of the study.

When we compared the effects of switching to IQOS to that of smoking abstinence, overlaid in green, we see that the levels of carboxyhemoglobin almost overlaps those of smoking abstinence.

Although the reduction in acrolein in the IQOS aerosol is

less pronounced than that of carbon monoxide, the reduction in exposure is still significant.

NNK and NNN, two carcinogenic tobacco-specific nitrosamines, are reduced by over 95% in IQOS aerosol compared with cigarette smoke. In both cases, the exposure is significantly reduced compared with ongoing smoking and approaches that of smoking abstinence.

When we look across all the biomarkers of exposure that were measured in the clinical studies, both in the U.S. and Japan, the results show that in smokers who switched to IQOS, there was a significant reduction in all 15 biomarkers of exposure and that these reductions approached those in smokers who abstained from smoking for the duration of the study. In fact, switching to IQOS achieved almost 90% -- 95% of the overall reduction in exposure achieved by smoking abstinence, where smoking abstinence is the maximum achievable reduction in exposure.

With this, we have demonstrated that smokers who completely switch to IQOS are exposed to significantly lower levels of toxicants than smokers who continued to smoke cigarettes.

In the causal chain of events, a reduced exposure to

toxicants leads to a reduction in molecular changes. Let me show you the effects on molecular changes observed when switching to IQOS.

We conducted a study in ApoE double-negative mice because this model reproduces the key aspect of atherosclerotic plaque formation and emphysema development in ways similar to humans, which includes the role of inflammation.

The study included a group exposed to cigarette smoke for 8 months at the dose corresponding to 30 cigarettes per day; a second group that was first exposed to cigarette smoke for 2 months and then switched to IQOS aerosol for the remaining 6 months at the equivalent of 30 HeatSticks per day. Similarly, the third group of mice was first exposed to cigarette smoke for 2 months and then switched to fresh air for 6 months, representing the smoking cessation benchmark. In addition, we also exposed a group of mice to IQOS aerosol for the entire 8 months of the study and a group to fresh air for the duration of the study.

The number of animals per group and dissection time point was based on the analysis of previous studies and selected to deliver enough statistical power to allow comparisons between groups.

We measured molecular changes using state-of-the-art technologies that allow for the quantification of both protein and gene expression levels.

The results of this study show that exposure to cigarette smoke causes massive changes in protein abundance, here on the left, where the darker color represents the higher level of change and asterisks indicate statistically significant values with p-values below 0.05, and gene expression levels here on the right, depicted as the volcano plots, where the larger the eruption, the higher the number of significant changes. In fact, the colored dots above the horizontal line indicate differential gene expressions that are statistically significant with false discovery rates of 0.05 or better.

When we look at the data for the group of mice that were switched to IQOS after 2 months of cigarette smoke exposure, we see that the changes in molecular expression are significantly attenuated and approached the levels seen in the group of mice that were switched to fresh air, the cessation group.

As you see on the left, the abundance of inflammatory proteins is strongly reduced following switching and cessation. Similarly, on the right, the high degree of gene expression changes induced by smoke exposure are strongly attenuated in

both switching and cessation groups.

In the group that was exposed to IQOS aerosol for 8 months, we only see very limited changes in both protein abundance and gene expression.

This shows that the reduction in exposure to toxicants achieved by switching from cigarette smoke to IQOS aerosol leads to a significant reversal in the molecular changes induced by cigarette smoke. In the causal chain of events, a reduction in molecular changes leads to a reduction in the disruption of biological mechanisms.

Let's now look at the effect of switching to IQOS.

The molecular changes caused by exposure to cigarette smoke leads to the disruption of a wide range of biological mechanisms such as cell stress, inflammation, and cell death. All of these are known to be associated with smoking-related disease.

To walk you through a sample of the data, I am presenting the results for inflammation. In the figure, you see that cigarette smoke exposure causes massive lung inflammation. Switching to IQOS and cessation both lead to significant reductions in inflammation. It is also important to note that 8 months of exposure to IQOS aerosol caused only minimal

inflammation.

To confirm these results, we measured the abundance of a number of inflammation markers in the bronchoalveolar lavage fluid, or BALF, of the animals. For example, interleukin-1 beta, interleukin-6, KC, and MCP-1 are increased by cigarette smoke exposure, on the red lines, but not by IQOS aerosol, the purple lines. Switching to IQOS aerosol, the orange lines, reduces the abundance of these markers in a way that is similar to cessation, on the green lines. Importantly, these inflammation markers have been reported to be more abundant in the BALF of human smokers than nonsmokers.

Results for the other biological mechanisms look very similar and lead to the same conclusion across all mechanisms affected by smoke exposure. This includes cell stress, cell proliferation, cell fate and apoptosis, and tissue repair and angiogenesis.

Let's now see how these results are supported by our clinical studies.

No single clinical risk endpoint, on its own, is predictive of the risk of smoking-related disease. Because of this, we measured a set of endpoints known to be affected by smoking and to reverse upon cessation in the 90-day clinical

studies I presented earlier.

To assess the changes upon switching to IQOS, we first have to understand how these endpoints are affected by cessation because we know that cessation is definitively linked to the reduction in risk for smoking-related disease.

The changes in clinical risk endpoints that we measured in smokers who abstained for the duration of the studies are small, which is expected in a healthy study population. Yet their direction is consistent with the literature on cessation.

Because these changes occurred upon smoking abstinence, which is known to reduce the risk of smoking-related disease, these changes are actually clinically relevant. They are indicative of the positive effect of cessation across a broad range of mechanisms, such as inflammation and oxidative stress, that are linked to multiple smoking-related diseases.

In both studies, we observed that switching to IQOS led to positive changes in clinical risk endpoints compared with continued smoking. The changes after switching to IQOS were consistent with the direction of change expected from smoking cessation studies and were of a similar magnitude to the clinically relevant changes observed in participants who abstained from smoking. The consistency of these changes

across the disease-relevant mechanisms are coherent with the multitude of positive changes that we observed in the ApoE study.

Together, the results from the in vivo and clinical studies show that switching to IQOS leads to a reduction in the molecular changes caused by smoke exposure and reduces the disruption of a broad range of biological mechanisms that are linked to smoking-related disease. In the causal chain of events, a reduced disruption of biological mechanisms leads to a reduction in cell and tissue changes.

Let's now look at how switching to IQOS affects these changes.

The mechanistic disruptions observed in smoke-exposed mice led to several changes at the cellular and tissue level. For instance, the number of inflammatory cells in the lung -- in particular neutrophils -- is massively increased following smoke exposure, while switching to IQOS rapidly reduces these changes, as does cessation. Eight months of exposure to IQOS aerosol did not induce significant inflammatory cell changes in the lung.

This slide shows that the results on lung tissue damage followed the same pattern.

This shows that switching to IQOS leads to a reduction in changes at both the cellular and the tissue level. In the causal chain of events, cellular changes and tissue damage caused by smoke exposure eventually lead to the development of disease. Because cessation normalizes these changes and attenuates the progression of tissue damage, cessation will also lead to a reduction in disease manifestation. Switching to IQOS should therefore also lead to a significant reduction in disease risk. I will now show you what we observed when switching to IQOS.

The results of our in vivo study show that cigarette smoke exposure leads to an increase in disease endpoints. Here we see that cigarette smoke causes extensive emphysema in the lung, while switching to IQOS led to a significantly reduced progression of emphysema score. The effects of switching approached those of cessation, and continuous exposure to IQOS aerosol did not cause emphysema. These results were further confirmed in our A/J mouse study.

This slide shows that cigarette smoke accelerates the growth of atherosclerotic plaque in the aortic arch, while switching to IQOS significantly attenuated plaque growth. For this endpoint, the effect of switching also approached that of

cessation, and continuous exposure to IQOS aerosol had a limited effect on atherosclerotic plaque growth.

Adhesion of neutrophils to the vascular endothelium is a critical early step in atherosclerotic plaque formation. To further support these in vivo results, we used a cell-based assay measuring the adhesion of human monocytic cells to primary human aortic endothelial cells. This study shows that IQOS aerosol causes 10- to 20-fold less monocytic cell adhesion to endothelial cells than cigarette smoke.

Let's now consider the totality of the evidence in the context of lung cancer.

Several lines of evidence point to the potential of IQOS to reduce the risk of lung cancer compared to cigarettes. Balkwill and Mantovani postulated that both genetic damage and inflammation are key contributors to cancer. In the context of smoking, this means that genetic damage and tumor initiation are caused by carcinogens. In parallel, inflammation, which promotes tumor progression and invasiveness, is caused by toxicants as well as carbon-based nanoparticles. Together, these mechanisms lead to cancer. This raises three key questions in the context of IQOS.

First: Does switching to IQOS reduce genetic damage?

Second: Does switching to IQOS reduce inflammation?

And third: Does switching to IQOS therefore lead to a reduction in lung cancer risk?

Let's first review the evidence related to genetic damage.

The emission of carcinogens is reduced by over 90% by IQOS compared to cigarettes. This led to a significant reduction in carcinogen exposure, a significant reduction in genotoxicity of the IQOS aerosol in standard cell-based assays, as well as a significant reduction in urinary genotoxicity of the clinical study participants who switched to IQOS compared with those who continued to smoke, a significant reduction in DNA damage measured in normal human bronchial epithelial cells. It also led to a significant reduction in the activation of the DNA damage repair mechanism in our animal studies.

The significant reduction in carcinogen exposure, especially for the polycyclic aromatic hydrocarbons, or PAHs, also led to a significant reduction in the activation of xenobiotic metabolism as evidenced by gene and protein expression data in cell-based assays, animal studies, and our clinical studies.

Taken together, our results demonstrate that IQOS causes less genetic damage than cigarette smoke. This indicates that

IQOS is likely to cause less tumor initiation than cigarette smoke.

Before I review the evidence on lung inflammation, let me come back to the carbon-based nanoparticles that are present in cigarette smoke but absent in IQOS aerosol.

There is a visible color difference when comparing the lung of mice exposed to cigarette smoke and IQOS aerosol. We believe that this difference is due, at least in part, to the persistent deposition of carbon-based nanoparticles from cigarette smoke.

Purified carbon-based nanoparticles, as well as cigarette smoke, have been demonstrated to trigger inflammation, including the production of interleukin-1 beta, interleukin-6, KC, and MCP-1 in nonclinical studies. Human data reported in the literature confirmed this mechanism. The BALF of smokers contained significantly increased levels of interleukin-1 beta, interleukin-6, interleukin-8, and MCP-1 as well as macrophages and neutrophils, compared with the BALF of nonsmokers.

This type of inflammation is known to promote tumor progression and invasiveness. In animal models devoid of the interleukin-1 beta gene, tumor progression and invasiveness are reduced. More recently, in humans, it has been shown that

canakinumab, an antibody against interleukin-1 beta, can reduce the incidence of mortality and -- incidence and mortality of lung cancer in a dose-dependent manner. This confirms the role of interleukin-1 beta in tumor progression and invasiveness.

Let's now review the evidence from our assessment program related to lung inflammation.

Toxicant emission is reduced by 90% by IQOS compared with cigarettes, and the IQOS aerosol does not contain carbon-based nanoparticles. This leads to a significant reduction in toxicant exposure and no exposure to carbon-based nanoparticles.

This reduction in exposure led to a reduction in lung inflammation. Specifically, our animal study results demonstrate IQOS aerosol causes significantly less lung inflammation than cigarette smoke. For instance, interleukin-1 beta is not induced by IQOS exposure, while switching and cessation both led to a similar reduction in IL-1 beta abundance in the BALF of the ApoE mice.

Taken together, our results demonstrate that IQOS causes less inflammation that cigarette smoke. This indicates that IQOS is likely to cause less tumor progression and invasiveness than cigarette smoke.

Because IQOS has a reduced impact on both key mechanisms involving cancer, as postulated by Balkwill and Mantovani, it can be reasonably inferred that it will also reduce the risk of lung cancer compared to cigarettes. We are completing the evaluation of the A/J mouse study, which will provide further evidence for the reduction in lung cancer risk.

Taken together, these results show that switching to IQOS can reduce the risk of tobacco-related disease.

With that, we have covered the evaluation of IQOS along the causal chain of events linking smoking to disease.

Before I conclude, let's consider the totality of the evidence collected by our multi-step evaluation of IQOS.

First, the IQOS aerosol contains 90 to 95% lower levels of toxicants than cigarette smoke and no solid carbon-based nanoparticles.

Second, this reduction in emissions leads to a reduction in exposure of human subjects who completely switched to IQOS and achieves almost 95% of the reduction induced by smoking abstinence where smoking abstinence is the maximum achievable reduction in exposure. A similar reduction in exposure is achieved in both animal and cell-based systems at equivalent nicotine concentrations.

Third, this reduction in exposure leads to a generalized reduction in molecular changes in all animal studies. Importantly, in the ApoE switching study, these reductions approach those induced by cessation and reflects the 90 to 95% reduction in toxicant exposure. Similar changes were also observed in cell-based studies. And in our 90-day clinical studies, clinical risk endpoints affected by smoking show favorable changes upon switching to IQOS in a way that is similar to those induced by smoking abstinence.

Fourth, this reduction in molecular changes leads to a generalized reduction in the disruption of biological mechanisms in all animal studies. In the ApoE switching study, these reductions also approach those induced by cessation and reflect the 90 to 95% reduction in toxicant exposure and molecular changes. In cell-based assays, we also observed a generalized reduction in the disruption of biological mechanisms.

Fifth, this reduction in the disruption of biological mechanisms leads to a reduction in cell and tissue changes in all animal studies. In the ApoE switching study, these reductions also approach those induced by cessation and reflect the 90 to 95% reduction in the disruption of biological

mechanisms from the previous step. In cell-based studies, a generalized reduction in toxicity was also observed.

Lastly, these reductions in cell and tissue changes lead to a reduction in disease endpoint in both ApoE switching study and the chronic exposure study conducted in A/J mice. The reductions again approach those induced by cessation in the switching study.

In conclusion, IQOS emits toxicants and is not risk free. Nevertheless, IQOS emits significantly lower levels of toxicants than cigarettes.

The results of all our studies across the causal chain of events are coherent with this reduction in toxicant emission and consistently demonstrated IQOS aerosol is less toxic than cigarette smoke. Therefore, the totality of the evidence clearly demonstrates that IQOS presents less risk of harm and tobacco-related disease than cigarettes. This supports the marketing order with the proposed messages.

Thank you for your attention. I will now hand over to Antonio Ramazzotti.

DR. HUANG: Actually, I think we might take a break now, but I did want to see if there are any Committee questions for Dr. Gilchrist or Dr. Peitsch. And we will have opportunity

also later.

Okay, Dr. Weitzman.

DR. WEITZMAN: So if you'll allow me, I have a number of questions.

DR. HUANG: Okay, how about we take a break then first, and then we'll get those questions.

Okay, so let's see. Before we break, I do want to announce people can order their lunches at the kiosk at the back so they will be ready for pickup when we break for lunch. So we're going to take a 15-minute break, and please remember, Committee members, that there must be no discussion of the meeting topic either amongst yourselves, with the press, or with any member of the audience. So we'll reconvene at 10:16.

(Off the record at 10:03 a.m.)

(On the record at 10:25 a.m.)

DR. HUANG: As we mentioned before the break, we just want to have the opportunity for clarifying questions only regarding the presentations up to now. So we will have much more time for discussion and other questions later. But at this point, are there any clarifying questions regarding the two presentations that we've just seen?

Yes, Dr. Weitzman.

DR. WEITZMAN: So were any of the studies, the data from which you presented this morning, did they involve child mouse models or all adult mice? That's the first question.

DR. PEITSCH: No, the studies involved mice the age of 6 weeks and then obviously aging as we go, as they go over to the 8-month time point.

DR. WEITZMAN: And from Dr. --

DR. PEITSCH: But not younger. Excuse me.

DR. WEITZMAN: Right. And from Dr. Applebee's presentation, the mandate seems to be -- I got the name wrong?

UNIDENTIFIED SPEAKER: Apelberg.

DR. WEITZMAN: Apelberg. I apologize.

(Laughter.)

DR. WEITZMAN: It's not the only mistake that I'll make today.

From his mandate, there were a number of mentions of epidemiologic studies. All the data that were presented were from animal studies. We are not going to hear any data about human studies with comparable sorts of endpoints?

DR. PEITSCH: We have conducted four exposure reduction studies. In these exposure reduction studies, we have done the exposure reduction through the biomarkers of exposure, and in

the 90-day studies we've also measured these clinical risk endpoints. In humans, yes. But we don't have, at this point, lower results from a longer study, and we could not have epidemiological study results with IQOS because we have it on the market for only 2 years in Japan, which was one of the first markets where we were present.

DR. WEITZMAN: Thank you.

DR. HUANG: Okay, any other clarifying questions? And, again, we will have opportunity for much more questioning later on.

Okay, Dr. Rees.

DR. REES: I was wondering, the toxicological studies that you presented, the comparator product, conventional cigarette, was 3R4F; is that correct?

DR. GILCHRIST: Correct, that's correct.

DR. REES: How does the toxicological profile of 3R4F compare with Marlboro cigarettes, say Marlboro Lights, one of the leading brands in the U.S. market?

DR. PEITSCH: On the chemistry point, 3R4F turns out to be very similar to a mid-American brand or blend, and from a toxicological study point, the results are very similar. In fact, if you use a branded tobacco product or 3R4F in the

toxicological study, such as, for instance, a 90-day innovation study, you will have very, very similar results.

DR. HUANG: Okay. Yes, Dr. Fagan.

DR. FAGAN: Just a follow-up question for the 3R4F. Did you use a menthol version of that as well, in your testing?

DR. PEITSCH: Yes, in one of the two 90-day innovation studies, we actually manufactured a test cigarette that has the same blend composition and, you know, physical attributes as the 3R4F and added menthol at two levels so that we could actually compare 3R4F with a 3R4F mentholated at two levels of menthol and then with the IQOS aerosol at three different doses.

DR. HUANG: Oh. And Dr. Fagan, one more.

DR. FAGAN: So, thank you. The menthol version was used for the studies that we just saw and that were just presented?

DR. PEITSCH: In the studies where we compared the menthol IQOS, mentholated IQOS, yes.

DR. HUANG: No other clarifying questions then -- oh, one more.

Dr. Wanke.

DR. WANKE: Dr. Gilchrist, I have a question about the sensors and the circuits. You said that the sensor controls

the -- senses the heat and controls and maintains a minimal temperature, an optimal temperature. Is there anything else that is controlled other than just the temperature? Does it control nicotine delivery or any other of the characteristics of the device?

DR. GILCHRIST: No. In fact, nicotine delivery is a natural consequence of the temperature and the makeup of the tobacco. Based on chemistry and physics, it delivers the level of nicotine that we measure in the aerosol. So the primary focus of the sensor is on maintaining the temperature profile within the set limit over the duration of the experience. Now, we can also use it to count the number of puffs. As you saw in the graph, there were a number of dips, and so the sensor helps to count those puffs and ensure that we finish the experience after either 6 minutes, which is when the battery will stop, or after 14 puffs, when it will be cut off because of the sensor.

DR. WANKE: And so you said that it's also stored in the memory. So what information is stored in the memory other than the puffs?

DR. GILCHRIST: It's basically the calibration information for each and every blade. So we go through a calibration process and store the information within the permanent memory

of each device so that it always maintains within the calibrated range.

DR. WANKE: And it's individualized per user, then? Each device individualizes --

DR. GILCHRIST: Per device.

DR. WANKE: Per device.

DR. GILCHRIST: There's no changes that a user can make. Once it's left the factory and calibrated, there's no way that a user can make any changes to the firmware to change the heating profile.

DR. WANKE: Okay, thank you.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Just to follow up on that, are there any other sensors in the device that do anything else?

DR. GILCHRIST: No, I don't believe there are. No. No.

DR. GIOVINO: Okay, thank you.

DR. GILCHRIST: We have a failsafe mechanism for the battery, so something that will prevent the battery from exploding in cases and overheating issues, so it will trigger a failsafe mechanism, but --

DR. GIOVINO: I haven't heard any press reports of the battery exploding like, you know, you hear with e-cigs. Has

exploding batteries ever been a problem?

DR. GILCHRIST: No, we have -- we sold, I think, 12 million kits worldwide. Up until now, we've never had a single incident of an exploding battery.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: I'd like to follow up on Dr. Fagan's question and ask Manuel, when you used menthol in your studies, were the results similar to what you just presented? Did menthol have an impact?

DR. PEITSCH: In the toxicological studies -- actually menthol did not display an effect on the toxicology; it did not display an effect on the exposure, that means the actual absorption of the toxicants that we've measured in the urine of the animals. So both at the level of exposure as well as at the level of the actual toxicological endpoints, we do not see a difference.

DR. HUANG: Dr. Rees.

DR. REES: I don't think you told us the temperature of combustion of the recon substance in the HeatStick. Is it the same as the blend in a conventional cigarette?

DR. GILCHRIST: No. In fact, it's -- we use the cast leaf process to create the homogenous tobacco that we need to use

within the HeatStick, but it's not recon as you would think of it in a conventional cigarette. So we use specially selected tobacco leaves that are ground into a powder, made into a paste, and then dried. And we do that simply to create a very stable and predictable aerosol from the tobacco so that we can have reliability over and over again through each puff, each stick.

DR. REES: So is the temperature of combustion the same as the blend in a conventional cigarette?

DR. GILCHRIST: So the HeatStick tobacco doesn't ever combust because we're well below the temperature where combustion processes take place, which is about 400 degrees centigrade -- Celsius.

DR. REES: What is the temperature of combustion for the substance in the HeatStick?

DR. GILCHRIST: So combustion processes can begin above 400 degrees Celsius, but a combustible cigarette will normally burn between about 6- and 900 degrees Celsius.

DR. REES: I still don't know what the temperature of combustion of the substance in the HeatStick is. Can you give us that information?

DR. GILCHRIST: I'm not sure I fully understand the

question. Because it doesn't burn, so we don't have any combustion happening.

DR. REES: At some temperature it must combust.

DR. GILCHRIST: So if you were to set a HeatStick on -- to light a HeatStick with a lighter, you mean? Yeah, then it would burn in the same way as a combustible cigarette. But obviously, that's not the intended way that the HeatStick should be used. It's intended to be used with the IQOS holder, which will heat it to within that controlled temperature range. In fact, maybe I can just add something. We have done experiments where we've looked at the chemistry if a consumer were to inadvertently light the HeatStick, in a case of misuse, and we see that the aerosol chemistry or the smoke that's delivered from IQOS, once it's burned, is very similar to what we find in a combustible cigarette. So it's no different when it's burned in that way, but that would be a case, obviously, of misuse.

DR. HUANG: Maybe we'll have one more clarifying question, and then we'll move on.

Dr. Thrasher, did you have a question or -- oh, okay.

Oh, Dr. Wanke.

DR. WANKE: One of the comparison groups that we didn't

see is for dual users. Will we be seeing the data for either the toxicology or the health effects of dual users?

DR. GILCHRIST: Yeah, we have focused our analysis on the population who fully switched to the product, and I think that's done quite deliberately because we wanted to understand what the maximum level of exposure reduction, for example, would be and also the maximum level of changes that could be expected in the clinical risk endpoints.

Nevertheless, we have looked at what happened in a dual-use situation, but because the sample size within the dual users was relatively small, because they dual-used with different use patterns, we cannot make firm conclusions about it. But I can ask my colleague, Gizelle Baker, to come and describe the results that we see, if that would be helpful. If we have time.

DR. HUANG: I'm sorry, we have our participant on the phone. Dr. Ossip had one question, so since she's on the phone, I'll allow that.

Dr. Ossip.

DR. OSSIP: Thank you. I noted that in your report that you submitted, you note that there are particular constituents that were higher in the IQOS compared to the comparator

combustibles, and I wonder if you were planning to speak more about that, or if not, if you could say something about that now.

DR. GILCHRIST: So Manuel is the best expert to answer that.

DR. PEITSCH: Yes. Yes, we found 53 in the regular HeatStick. We found 53 constituents that are either higher, 50, of unique, 3, to IQOS compared to the 3R4F smoke. So if I can have Slide 1 up, please. Back to looking at this slide here, what we see is that among those constituents which we analyzed from a toxicological evaluation standpoint, we found four that had a concern in the context of carcinogenicity. And we then looked at the data from the inhalation toxicology and calculated that the exposure from 40 -- consuming 40 HeatSticks per day would be below the threshold of concern that would be derived from the inhalation toxicology.

Important for me in this context is that when we look at the carcinogenicity of the aerosol, if I can have Slide 1 up, please, we see that the Ames test, in itself, is negative across -- first of all, there is no mutagenicity in the vapor phase, but second, in terms of the TPM, the total particulate matter, we have also negativity in the Ames test.

Now, the Ames test is not covering the full range, obviously, of constituents. There are constituents that are, by themselves, not really detected, carcinogenicity not detected by Ames test. This is why we conducted a second test, which is the mouse lymphoma assay. And if I could have Slide 2 up, you'll also see that we have a drastic reduction in genotoxicity.

Thus, all taken together, all this information together, shows us that the additional compounds or those which are higher in the aerosol of IQOS compared to the 3R4F smoke are, in themselves, in aggregate not increasing the risk of this, of the IQOS aerosol.

DR. OSSIP: Thank you. And could you just remind us over what period of time was this measured?

DR. PEITSCH: Well, we have two arms here really. If you're talking about the biological test, those are cell-based assays which follow in the toxin OECD guidelines, and basically these are, you know, regulated assays that we perform on the GLP. So it's not really that they're measured around a particular timeline, but we know, for example, in the MLA, that we measure at 4 hours as well as at 24 hours.

If you're talking about the aerosol analysis, this is done

by a differential screen. We're looking at all the peaks in high-resolution mass spectrometry, and then we're deducting from that all the peaks from IQOS. Those are the peaks, then, which are different between the two aerosols and the IQOS -- sorry, the IQOS aerosol compared to the 3R4F smoke. So this is really an analytical chemistry process using high-resolution technology.

DR. OSSIP: Thank you.

DR. HUANG: I think we will move on with the presentations. And again, we will have quite a bit more time for further discussion even on these presentations.

So I think next is the Population Health Benefit - Perception and Behavior.

Dr. Ramazzotti.

MR. RAMAZZOTTI: Good morning. Just a few seconds to go back to presentation mode.

(Pause.)

MR. RAMAZZOTTI: A few seconds.

(Pause.)

MR. RAMAZZOTTI: Okay, we're ready to go. Good morning, everyone, and thank you. To start, I would like to go back to the statute for a moment.

Manuel has shown that IQOS presents less risk of harm and tobacco-related disease, as required by Part A of the statute. The assessment then turns to Part B.

As the statute directs, we have examined the likelihood and manner of IQOS use among both smokers and nonsmokers. We seek to maximize the number of adult smokers who switch exclusively to IQOS. At the same time, we want to minimize the likelihood of decreasing cessation among smokers or increasing initiation among nonsmokers. In short, this is the optimal regulatory outcome and the opportunity that Moira's diagram depicted earlier.

My focus is on our consumer perception and behavior program, or PBA program as we call it. This work helps us assess who will use IQOS and to what degree. Our PBA program tracks the FDA draft guidance for modified risk products and reflects advice from experts in the field of behavioral, regulatory, and tobacco research. We look to best practices from other product categories that FDA regulates, such as over-the-counter drugs.

We carried out nine U.S. studies involving both qualitative and quantitative research. More than 11,000 people in the U.S., including smokers and nonsmokers, participated in

this research. We have developed a strong evidence base to support the modified risk applications. This evidence will, of course, be further supported by postmarket surveillance and studies should IQOS be authorized.

Out of the nine studies, our PBA program included six to develop and assess the IQOS communication. These qualitative and quantitative studies were conducted in two phases. In Phase 1, we explored different product messages conveying the product benefits that our science substantiates, as Manuel just described. We investigated how each element of the different messages contributed to comprehension of the modified risk information, intent to use, and risk perception.

In Phase 2, we assessed the proposed label, labeling, and advertising in terms of consumer understanding and estimated intent to use among smokers and nonsmokers.

As a result of our Phase 1 work, we selected and tested three product messages with either the Surgeon General's warnings or the PMI warning that we developed. The PMI warnings were developed to reflect the characteristics and the risk profile of IQOS and were used in the PBA program for testing purposes. To be clear, we do not propose replacing the Surgeon General's warnings with the PMI warning.

In Phase 2, we conducted three studies to assess communication materials, one for each of the product messages which are part of our submission. In each study we enrolled approximately 2,200 participants. We included smokers, both with and without the intention to quit, former smokers, never smokers, and legal age to 25 never smokers. The sample was balanced by smoking status, sex, age, and city. Each study was conducted in four cities, one in each of the U.S. census areas.

Each participant was randomized to one of the tested materials, which was given as a physical mockup. The brochure and the HeatStick packs carried either one of the four Surgeon General's warnings or the PMI warning. The direct mail was tested only with the PMI warning.

The hypothetical price for IQOS was $79.99, and the price for a pack of 20 HeatSticks was equal to the price of a pack of Marlboro cigarettes in each city where the research took place.

Let's look at one of the product messages as actually tested in Phase 2.

In this slide you see the product message that "IQOS presents less risk of harm than continuing to smoke cigarettes" on a pack of HeatSticks. The pack on the left includes one of the four Surgeon General warnings. The pack on the right

includes the PMI warning. I will now show you data on comprehension of this product message.

This slide shows that the majority of participants, including both adult smokers and adult nonsmokers, correctly comprehended the reduced harm message with each warning, 73% with the Surgeon General warning and 78% with the PMI warning. Notably, only 1 and 2% misunderstood the message as stating there to be no risk of harm.

The results of this study show the majority of participants understood that IQOS presents less risk of harm but is not risk free. These results are representative of what we observed for the two reduced risk messages across all tested communication materials.

Now let's turn to likelihood of use. To assess intention to use, we showed communication materials to the study participants. Here you can see an example of the results among adult smokers who reported no intention to quit when presented with a HeatStick pack carrying either the Surgeon General's warning or the PMI warning. Twenty percent of adult smokers expressed a definite or very likely intention to use IQOS with the Surgeon General warning, and 28% did so for the product bearing the PMI warning.

Across all tested product messages in communication studies, we observed that this group of smokers consistently showed an overall positive intention to use IQOS in the range between 20 and 39%.

The next step was to measure how this level of intention to use translates to actual use. We observed this through our actual use study. Before showing you the key results, let me briefly describe some aspects of the study methodology.

The purpose of the actual use study was to investigate how adult smokers might use IQOS in the real world. The sample included more than 1,000 participants in eight cities geographically spread across the U.S. and approximated the adult smokers distribution in terms of sex, age, race, and income.

At enrollment, participants were shown a physical brochure containing the product message that "IQOS can reduce the risks of tobacco-related diseases." Participants were free to consume cigarettes, IQOS, and any other product containing nicotine, ad libitum, as they would in real life. Daily consumption of IQOS and cigarettes was reported via an electronic diary. The study design included a 1-week baseline period, a 6-week observational period, and a 1-week closeout

period.

At the end of the 6-week observational period, 15% of participants had become exclusive or predominant IQOS users. The proportion of exclusive IQOS users was stable as the majority of participants who switched did so within the first 3 weeks. These are encouraging results considering the premarket setting in which the actual use study was conducted. For example, we exposed participants to the product message only once, and they did not receive coaching reiterating the benefit of complete switch.

We can look to this study as one way to gauge the magnitude of opportunity in the U.S. The observed 15% switching rate could translate to approximately six million smokers switching to IQOS.

During the actual use study, we collected data about consumption of IQOS and cigarettes. Across all IQOS use categories, there was minimal change in consumption of IQOS and cigarettes taken together between baseline and observational. Importantly, we observed that the daily cigarette consumption decreased for all IQOS use categories. The largest decrease was observed in participants who were predominantly or exclusively using IQOS at Week 6.

Let's now turn to data from countries where IQOS is already commercialized, which can provide useful insights about the acceptance of IQOS and how premarket information translates to postmarket results.

We have conducted premarket whole offer studies in five countries. The study design was similar to the actual use study conducted in the U.S.

On this slide you can see that 12% of participants in Italy and 30% in Japan switched to IQOS at the end of the observational period. These results indicate that there is a meaningful proportion of adult smokers who were likely to switch to IQOS in each country, and this is consistent with what we observed in the U.S., here presented on the right.

Let's focus now on postmarket results in Japan and in Italy. These results come from postmarket consumer panels that we have set up to monitor switching patterns over time. These are composed of adult smokers who have purchased IQOS and agreed to register as a member. We measured switching and patterns of use by categorizing IQOS users according to the same usage categories adopted in the actual use study.

These graphs show that exclusive use represents the most common behavior among IQOS purchasers. In August 2017,

exclusive use reached 72% in Japan and 61% in Italy, meaning they have successfully switched away from cigarettes. However, this is a static picture taken in August 2017. It is very insightful to look at how the exclusive pattern of use evolved over time by analyzing the switching behavior of different cohorts of IQOS purchasers in the past.

The data from Japan show that among those who purchased IQOS in September 2015, which is at the beginning of the national launch, 35% became exclusive users within the first 3 weeks from purchase. The proportion of exclusive IQOS users grew over time and reached 61% among the March 2016 purchase cohort.

Those data suggest that repeated communication, guided trials, and growing popularity of IQOS are major contributing factors in increasing awareness and encouraging adult smokers to reach exclusive use during the first week following purchase. We believe we would see similar dynamics in the U.S. should IQOS be authorized.

Let me now address the likelihood of decreasing cessation among smokers or increasing initiation among nonsmokers. I will start with the first: cessation.

We do not want to deter smokers from quitting. The best

choice to reduce the risk of tobacco disease is to quit tobacco use or nicotine altogether. In our PBA we identified current smokers who had an intention to quit either in the next 6 months or in the next 30 days. We included them into our communication studies to assess if the exposure to IQOS communication materials would impact their intention to quit.

The results of our studies indicate that the exposure to the IQOS communication materials minimally altered the reported intention to quit all tobacco. We believe these results indicate a low likelihood that IQOS will deter adult smokers from quitting. This is an area that will be carefully monitored through postmarket studies.

Let's turn to likelihood of increasing initiation among nonsmokers.

In our IQOS communication studies, we measured intent to use IQOS among nonsmokers. On this slide you see an example of the results for the message that "IQOS presents less risk of harm than continuing to smoke cigarettes" presented on the HeatStick pack. Within adult never smokers, positive intention to try was 0%, and within the legal age to 25 never smokers was between 1% and 3%.

When we looked across all studies and tested materials,

the levels of positive intention to try or use IQOS among adult never smokers were no higher than 2.1%. And for the LA to 25 never smokers, these were no more than 3%. This gives us confidence that adult never smokers will have a low interest in IQOS.

One of the main concerns for everyone is to what extent minors will start to use IQOS. We do not do research with anyone below the legal age for smoking. We also confirmed with FDA in advance that this would not be appropriate research for us to do.

The results of our IQOS communication studies show that the intention to try and intention to use among never smokers, including the young adult segment of legal age to 25 years old, was low. This, in combination with regulatory and commercial controls, such as age restrictions, advertising restrictions, postmarket monitoring, and enforcement authority, provide additional safeguards that should minimize this unintended use. We will discuss with the FDA ways to actively monitor this serious issue through postmarket surveillance should IQOS be authorized.

We also tested former smokers' intent to use IQOS. On this slide you see an example of the results from the same

study among adult former smokers. In this case, the levels of positive intention to try were 8% and 2%. Again, looking at all our studies assessing IQOS communication materials, we observed a low intention to try and use among adult former smokers, between 1% and 9.6%. These levels of intention to try and use IQOS indicate that former smokers are likely to have a low interest in IQOS.

From other qualitative studies, we have learned that there were three main reasons for the lack of interest in using IQOS: IQOS contains tobacco, it poses health risks, and it is addictive.

Generally, from never smokers, we heard comments such as they do not plan on ever smoking cigarettes or using tobacco of any kind on a regular basis. From former smokers, we heard that they do not want to use IQOS because it would mean going back to tobacco and they do not want to have anything to do with tobacco again.

The evidence base I've shared with you today indicates that IQOS will provide a benefit to the health of the population as a whole.

Both smokers and nonsmokers understood that IQOS presents less risk of harm or that IQOS can reduce the risk of tobacco-

related disease, but it is not risk free.

A meaningful proportion of American adult smokers will accept IQOS as a replacement for cigarettes and will use it exclusively.

The likelihood of decreasing cessation or increasing initiation is low and can be monitored, measured, and addressed in coordination with FDA's oversight.

Let me now turn it over to Sarah, who will speak about plans to introduce IQOS in the U.S.

Thank you very much.

MS. KNAKMUHS: Thank you, Antonio.

Good morning, my name is Sarah Knakmuhs. I'm Vice President of Heated Tobacco Products for Philip Morris USA, an Altria company. My role is to lead the commercialization efforts of IQOS in the U.S.

I'm here today to describe our plans to introduce IQOS to adult smokers in the U.S. I will address a few key topics, including how we will educate smokers about IQOS, how we'll encourage them to switch completely from cigarettes, and how we'll limit our reach to unintended audiences.

Under agreements with Philip Morris International, Philip Morris USA is licensed to sell IQOS in the U.S. after PMI

receives a marketing order from the FDA. We've been working with PMI since 2013 to support PMI's U.S. research and the preparation of its submission to the FDA.

During that time, we've also had the opportunity to learn from PMI's introduction of IQOS in markets outside the U.S. We're eager to bring IQOS to the United States, particularly given the scientific evidence supporting the harm reduction claims and the potential for adult smoker conversion demonstrated premarket in the U.S. and postmarket outside the U.S.

Today, FDA has the regulatory framework to permit companies to bring modified risk products to the market with accurate risk communications and to provide oversight and safeguards to keep those products out of the hands of youth. In fact, that's one reason Altria supported FDA regulation of tobacco through the Tobacco Control Act.

As we bring IQOS to the market, our focus is on the 40 million men and women who smoke in the United States. We believe IQOS could be the product of choice for many U.S. adult smokers, and our goal is to convert them to IQOS.

However, we recognize that IQOS and heat-not-burn technology are novel and unfamiliar to most U.S. cigarette

consumers. As PMI has learned internationally, encouraging a consumer to switch from combustible cigarettes to IQOS is not easy. It requires significant behavior change on multiple levels.

As you might expect, IQOS product use is different and therefore is aided by hands-on tutorial. Think of the first time you used a smartphone. Any electronic product has a learning curve and can be complicated to use at first.

Perhaps even more importantly, the taste of heated tobacco is different than that of burned tobacco. For someone who smokes, the initial taste of IQOS may seem unfamiliar. These changes require altering the behavior with which smokers are comfortable.

We have a challenge before us as we sell IQOS in the U.S. On one hand, we're committed to maximizing our reach to adult smokers and supporting them so they can switch completely to IQOS. On the other hand, we want to limit our reach to unintended audiences such as nonsmokers and youth. Our marketing approach is designed with these challenges in mind.

There are three components for the adult smoker: awareness, trial, and conversion.

First, we need to build awareness about IQOS to introduce

the adult smoker to a concept of a heated tobacco product and inform them of its reduced risk profile.

Second, we need to give them opportunities to try the product.

Finally, we need to support the IQOS consumers so they can convert, meaning switch completely from cigarettes to IQOS.

Let me give you a sense of how this approach might look in practice, along with the safeguards we will employ.

To raise awareness about IQOS in our launch market, we'll use tools such as print advertising, direct mail, and email. Print and digital advertisements will be placed only in publications with predominantly adult readership, following FDA's proposed guidelines. For direct mail and email, we will reach adult smokers by identifying them from our adult tobacco consumer database, which we have built over many years.

We use electronic age verification before we allow a name on that database, so we know we are reaching our intended audience. Electronic age verification allows us to compare personal information a consumer submits with a third-party database to confirm age and identity, not unlike the identity verification questions used by banks.

In comparison to raising awareness about IQOS, trial and

conversion requires a more involved approach. Every smoker is different, so these steps must be personalized to each individual consumer's needs.

Trial is more than a simple demonstration of the product. It's a conversation that begins with an accurate overview of the differences between heated versus burned tobacco. We provide a detailed tutorial of the device itself, and adult smokers are able to purchase a trial pack of HeatSticks. During this dialogue, we'll reinforce the importance of using IQOS exclusively to achieve its full benefits.

Finally, should they be interested in buying a device, we encourage them to register for post-purchase support.

This conversation is personal, not transactional, and needs to fit into each adult smoker's busy life. So we'll have these conversations with adult smokers through individual interactions, consumer events, and at retail. This face-to-face interaction requires age verification and identity at the outset. To have a guided trial, a consumer must confirm they are current smokers.

This individualized approach continues post-purchase because complete switching is the hardest part of the journey. So we'll provide a range of support options to help adult

smokers fully switch to IQOS. For example, a new IQOS user may get a friendly reminder email to clean and charge their device or a text message from an IQOS expert encouraging them to continue using HeatSticks, not conventional cigarettes.

Once again, we'll be able to limit our interactions to those we have age verified either through government-issued ID in person or by electronic age verification for those who have registered as IQOS users.

This entire approach is unique to IQOS. It requires commitment and patience, but we think it's the best way to convince smokers to switch to IQOS. Our approach is to drive awareness and conversion among adult smokers while limiting the reach to unintended audiences. Moreover, FDA has the authority to impose additional restrictions on the marketing and sale of tobacco products.

Beyond the marketing practices we'll use for IQOS, we will also work with PMI to monitor IQOS's impact through postmarket surveillance and studies. For surveillance, we'll use our call center to capture reports of adverse events. We will also conduct literature reviews, monitor regulatory reporting systems, and collect reports in the National Poison Data System. The results of this surveillance will be reported to

the FDA along with a summary of adverse events collected by PMI in its markets outside the U.S.

In addition, we'll be conducting studies to assess the impact of IQOS, including cross-sectional surveys and a longitudinal cohort study. These studies will be implemented as IQOS gains traction in the marketplace to assess prevalence, use behaviors, perceptions, and self-reported health measures. FDA will provide input into the postmarket surveillance program.

We look forward to the opportunity to bring IQOS to the U.S. cigarette consumers as a modified risk product. These opportunities come with responsibility to help adult smokers understand this product as an acceptable, less harmful alternative to cigarettes, to encourage them to switch completely from cigarettes to IQOS, and to implement safeguards to minimize reach to unintended audiences.

We acknowledge FDA's broad oversight and welcome the input as we take on this responsibility and monitor IQOS's postmarket impact.

Thank you for your time and attention. Now we'll have Moira return to wrap up the presentation.

DR. GILCHRIST: Thank you, Sarah.

I'll now address the final piece of data related to the impact on the population as a whole: population health impact modeling.

FDA acknowledges the difficulties in making premarket assessments for the population as a whole. They encourage manufacturers to develop and apply innovative models to make preliminary estimates.

Consistent with FDA's guidance, we developed, validated, and published a population health impact model using well-established methods in epidemiological modeling and simulation analysis.

The model incorporates two main components: the prevalence component and the epidemiological risk component. It's a counterfactual model based on the U.S. smoking population between the years 1990 and 2010.

The prevalence component establishes a hypothetical population of never, current, and former smokers based on publicly available databases and scientific literature. We applied transition probabilities to this hypothetical population, including initiation, relapse, and cessation.

We validated the prevalence component using actual smoking statistics for the corresponding time period. We used data

from the studies outlined by Antonio to develop and include IQOS transition probabilities.

The epidemiological risk component used the tobacco use histories generated by the prevalence component, together with estimates of the relative risk of developing ischemic heart disease, lung cancer, and stroke. And COPD, sorry. Together, these account for more than three-quarters of all smoking-related disease.

The model also incorporated the relative risk of IQOS use compared with cigarette smoking based on all of the evidence that Manuel presented. We validated the epidemiological risk component by comparing smoking-related deaths, predicted by the model, with data from the Surgeon General's report and other sources.

We conducted multiple simulations to estimate the impact of introducing IQOS in the United States. The simulations predicted that introducing a product with its claims would have resulted in a significant reduction in smoking-attributable deaths.

For our baseline simulation, we assumed that IQOS delivers 90% of the benefits of smoking cessation. This assumption is based on the science in our application, which Manuel

summarized. We assumed that 15% of the smoking population would switch to IQOS within 10 years based on Antonio's data. The model predicted that more than 90,000 smoking-related deaths could have been averted within 20 years of introducing IQOS.

We also ran simulations with more pessimistic assumptions. We wanted to identify events that would have to occur to overwhelm the public health benefit that could be achieved by introducing IQOS.

For this to happen, the introduction of IQOS with its product messages would have to cause millions of nonsmokers to start using combustible cigarettes and prevent large numbers of current smokers from quitting. Nothing like this has happened in any country where IQOS is available. In fact, it's quite the reverse. In Japan we're seeing dramatic decreases in cigarette sales following the introduction of IQOS. Recently published data from Japan showed that cigarette sales declined by more than 18% in 2017 compared with a historical decline of 3 to 4% per year. The only major change in the market was significant switching to heated tobacco products, predominantly IQOS.

No model can be perfectly precise, but these results

demonstrate the potential for major population health benefits over time.

The population health impact model combined with our perception and behavior assessment data, commercial and regulatory controls, and postmarket surveillance plans for the United States demonstrate that the likelihood and magnitude of IQOS benefiting the population as a whole is much greater than the opposite. If ongoing monitoring suggests that a different outcome is likely, FDA has authority to swiftly modify or withdraw product authorization.

With IQOS, meaningful change is possible. It's not a perfect solution, but the statute doesn't require perfection. It calls for change and progress. It enables real-world solutions that are better than the status quo.

There's no question that never starting smoking to quitting are the best options. But for those people who would otherwise continue to smoke, your recommendation can help FDA apply the powerful tools given by Congress to change the status quo -- millions fewer smokers, millions of changed lives, the potential for significant reductions in tobacco-related diseases, and an important step forward along the harm reduction pathway as called for by Congress and FDA.

Thank you, Mr. Chairman.

DR. HUANG: All right, thank you.

And so now we will open it up to questions, and all of the presentations are open for discussion. And we will also perhaps delay lunch, if we need it, for additional questions.

DR. GILCHRIST: Mr. Chairman, may I just interject? I will act as moderator for the questions because we have a panel of experts here, beyond the presenters, who can help answer any question the Committee may have.

DR. HUANG: Okay.

All right, Dr. King.

DR. KING: Yes, thank you.

So there's been a lot of talk about the intended audience, and I think it's important to relate to the unintended audiences, particularly youth. And, of course, in the current tobacco environment, the products are not intended for youth, but we have one in four, 4 million youth, using those products.

So that being said, the first question out of two is do you have any data on youth? And it sounded like you don't, and so I'm interested to know if there is any other data elsewhere, done by anyone else, that you're aware of, that has specifically assessed, you know, the patterns of use,

particularly dual use among the unintended audience.

And then my second question is, assuming the answer to that is no, have you stratified any of your analyses by age to see if you see a variation on particularly that young adult demographic from 18 to 24 who could presumably legally purchase the product? Is there variation in some of the parameters that you've assessed by age strata?

So those are my two questions.

DR. GILCHRIST: Okay. So the answer to the first one is a clear no, we do not do studies in youth by policy, but we did discuss this challenge with FDA prior to conducting our perception and behavior studies, and we decided that we would run studies in young adult population, oversampling the young adult population, to help inform what may happen in youth; but obviously, it's not a substitute for youth.

But we believe the collection of that data in a postmarket environment will be absolutely critical, and we look forward to discussing with the Agency and others what the best modality for gaining that data would be. But currently, no, we have no studies on youth.

And the second question, stratification by age, are you referring to the perception/behavior data or the clinical data?

DR. KING: Yeah, I think all of the above.

DR. GILCHRIST: Okay.

DR. KING: Do any of them have any stratification by age, particularly that young adult demographic?

DR. GILCHRIST: Okay.

DR. KING: I think that's what I'm looking for.

DR. GILCHRIST: So for the perception/behavior data, I'll ask Antonio just to come and give you an overview of some of the insights we saw in the young adult population.

MR. RAMAZZOTTI: So we indeed studied, as part of our PBA program, not just the full cohort of adult smokers but also specifically we had an oversample; we looked specifically at young adult never smokers or LA to 25 years old.

What we have seen consistently across all our studies where we interviewed these people is that there is a low interest in IQOS as expressed by intention to use. In fact, across all our communication studies, we interviewed 1,430 LA to 25 never smokers and -- intention positive, intention -- positive intention to try only among 12 of them and a positive intention to use only among 4 of them. So this is really the data that we have.

Now, we also have data from post-launch market in other --

in the markets where we have already commercialized, and what we see, for example, in Japan is that the typical IQOS user is 30 years of age, between 30 and 49 years of age. So that is also an additional corroboration.

DR. HUANG: And I think Dr. Weitzman has a question for following up on this.

DR. WEITZMAN: I'd like to address the question asked by Dr. King. While these datasets did not ask specifically about IQOS, they did ask about the electronic cigarettes. And so the National Adult Tobacco Survey, the National Youth Tobacco Survey, Monitoring the Future, the "truth" campaign's longitudinal study, and the PATH study, which is a longitudinal study, comes up with findings very different from what you've presented and have asked questions about intent to use and the transition from use of e-cigarettes to cigarettes. So there's a vast U.S. literature, both about youth and about young adults.

DR. GILCHRIST: So if I may add a comment on that. Of course, IQOS is not an electronic cigarette, and we understand the concern that the public health community has around youth uptake of electronic cigarettes. But IQOS is a very different product; it is subject to very different regulations, also,

than currently applied to electronic cigarettes and very different marketing approach as well, because of those regulations. So we believe that whilst we have to be absolutely mindful to ensure that youth uptake of the product does not occur, we believe that these controls can help to minimize the access of youth to IQOS in a way that just currently is not possible to do in the e-cigarette environment.

But certainly, that's something we're very aware of, and we look forward to discussing with the Agency how we can gather data to ensure that our assumption about youth access is borne out in the postmarket environment.

DR. HUANG: Dr. Fagan.

DR. FAGAN: So you mentioned that the intended audience is all U.S. adult smokers. Who is the target audience for Menthol Smooth and Menthol Fresh? And then I have follow-up question.

DR. GILCHRIST: So approximately anywhere between 35 and 40%, depending on which data you're looking at, of the U.S. adult smoker population chooses a menthol product. So we wanted to ensure that we had a product offering within the IQOS range that could suit the taste preferences of that segment of the population.

DR. FAGAN: Okay. So just my follow-up question is we

know that menthol is very -- the product itself is highly used among African-American smokers, women smokers, youth and young adult smokers, and also people of disadvantage. And so my follow-up question is for the communication studies and the studies on switching, what is the composition of the participants in those studies, and does the composition mirror that of who menthol smokers are in the U.S.?

DR. GILCHRIST: So we tried to replicate as close as possible the total U.S. smoking population, but very aware of the points that you brought up and very keen to ensure that we have a product offering for those particularly vulnerable groups that you mentioned. But Antonio can talk through some of the data that we have across the different subpopulations.

MR. RAMAZZOTTI: So, indeed, we interviewed adult smoker population in our studies, which was representative or balanced across different applicants. So when it comes to the IQOS communication studies, we balanced the sample by age, sex, and city. And when it comes to the actual use study, we balanced the sample across race, sex, age, and income. So we do have data across different stratification, and I can show you just one slide to give you some data about the demographics in our IQOS communication studies, as you asked. So can I have

Slide 1 up?

So this slide shows how across arms tested in the reduced risk of harm claims communication studies, how the sample was balanced. So as you can see, we have representation of different race, ethnicity, and educational level.

DR. FAGAN: Is this for Smooth and Fresh, though? Is this for the regular IQOS, or is this for the menthol versions? I want to know what the data are for the studies related to Menthol Smooth and Menthol Fresh.

MR. RAMAZZOTTI: Okay, this is about our communication studies where we showed communication material related to either the menthol product or to the regular product, depending on the taste preference that the consumer reported to have before coming to the study. And when it comes to the actual use study, we did indeed place or give access to the product according to the taste preference the consumer had. So we have data on both.

DR. FAGAN: Okay, so the demographics here are not necessarily representative of the population who uses menthol cigarettes. So my second question is, just again, to ask about the switching study.

MR. RAMAZZOTTI: Yeah.

DR. FAGAN: Who were the participants in your switching study related to Menthol Smooth and Menthol Fresh, and did you include menthol smokers, cigarette smokers in those studies on Menthol Smooth and Menthol Fresh?

MR. RAMAZZOTTI: So, yes, we did include menthol cigarette smokers in the actual use study, but we only placed the Menthol Smooth, and we didn't use the Menthol Fresh as part of the actual use study. So two variants were available for the actual use study, was the regular tobacco variant and the Menthol Smooth.

DR. FAGAN: And do you have the data that you can show us, the menthol smokers, cigarettes smokers who completely switch exclusively to Menthol Smooth? So that was the only -- okay.

MR. RAMAZZOTTI: Yes, we do have the data.

DR. FAGAN: Will we be able to see that at some point?

MR. RAMAZZOTTI: Yes, sure. And let me give my team a few seconds to pull up the slide about the switching by taste bias, and we'll be able to show it to you. So can I have Slide 2 up, please?

So this slide shows, in fact, the progression of adoption of IQOS across the 6-week observational period. Menthol is presented on the left of the slide, the regular product is

presented on the right of the slide, and the exclusive use reported at the end of the observational period was 6% for the regular product, 7.3% for menthol. The predominant usage was 5.8 versus 6.6.

DR. FAGAN: Is this for menthol to menthol? I'm asking a question about switching from a menthol cigarette to a menthol flavor --

MR. RAMAZZOTTI: Yes. This is, if you want in fact, menthol cigarette smokers who switched to menthol IQOS.

DR. FAGAN: So at Week 1, 8.7% of menthol smokers completely switched to a Menthol Smooth; is that correct?

MR. RAMAZZOTTI: Yes, it is correct. I mean, in Week 1, the menthol -- the consumers who received the menthol HeatSticks switched to IQOS Smooth Menthol, 8.1%.

DR. FAGAN: Okay, 8.1% of menthol smokers switched to a Menthol Smooth?

MR. RAMAZZOTTI: Yeah.

DR. FAGAN: Exclusively?

MR. RAMAZZOTTI: Yeah. That's correct.

DR. HUANG: Dr. Mermelstein.

DR. MERMELSTEIN: I have a couple of questions, one about the warning messages. Do you have a picture of how the message

on the pack actually looks and what you actually -- and what you showed participants in the studies? The actual visuals that they saw or --

DR. GILCHRIST: The team will just check just to see if we have a slide of that. Give me just a moment.

DR. MERMELSTEIN: And then a packaging question. Where do the labels go? So do people -- because on the device -- and you have the charger and the sticks, how is it all packaged? And where would the labels go, and what do they carry with them when -- you know, what does this look like? And how are they purchased, and where are those labels and --

DR. GILCHRIST: Okay. So if you're referring to the modified risk claims, the proposal was to put those on the pack and in other communication materials such as brochures, etc., that would be in and around the smoker.

DR. MERMELSTEIN: So when you say on the pack, the pack of what? Are these HeatSticks? Are they a pack of --

DR. GILCHRIST: Oh, sorry. The HeatSticks, yes.

DR. MERMELSTEIN: -- the HeatSticks?

DR. GILCHRIST: Yes. If we could get Slide 1 up, you can have a look at what the HeatStick pack would look like, on the back face of the pack.

DR. MERMELSTEIN: So there's no label on the device itself or the charger. And then do people have to carry a pack with -- I mean, can they take things out of the pack and put them with the device and the charger? How does that all fit together? How are people -- what do they do with all of this? Is there a carry pouch? What do they do?

DR. GILCHRIST: I can tell you from personal experience. So, obviously, there's a bit more to carry around than just a packet of cigarettes and a lighter. So you have the holder that's placed inside the charger, so you have one unit that's roughly the size of a mobile phone, and you have a small pack of HeatSticks that you have to carry in addition to that. So some people place them in the pocket, some people create a little pouch to carry them around, but it's possible to carry it with you for the duration of the day without any discomfort.

DR. HUANG: And I do have a follow-up just on the labeling. And you talked about the results in Japan. Does Japan have a modified risk tobacco product labeling on their product?

DR. GILCHRIST: They do not have a regulatory process. The United States is currently the only regulatory regime that exists for modified risk tobacco products in the form that it

exists here. Nevertheless, we are making some claims that here in the United States would require approval by the Food and Drug Administration, but because of the law in Japan, it's not required.

And we're using very focused ways to help smokers to understand what those claims mean and what they don't mean, and the results from that have been very encouraging. Smokers understand what the messages are, and they cite them as reasons why they're switching and also reasons why they're sticking with the product, too.

DR. HUANG: And one thing, we do have -- I think this might be an appropriate time. We do have an actual product, is that right, that we can have people look at?

DR. GILCHRIST: Yes. Yes, we provided one, too.

DR. HUANG: We can pass that around.

All right, Dr. Thrasher.

DR. THRASHER: Thank you.

So with regard to the switching rate of 15 that then gets plugged into the model, as I understand it, eligibility for that study involved smokers indicating that they were interested in using IQOS in the first place.

DR. GILCHRIST: Um-hum.

DR. THRASHER: And so presumably, that 15% number that you're using from Week 6 is actually lower when you consider the full range of smokers who would include those who were not interested in using IQOS. Do you have any data to suggest kind of what that real number looks like when you consider those smokers who are not interested in using IQOS? And I have a follow-up question after that.

DR. GILCHRIST: Okay. Well, we understand the limitations. It is impossible to powerfully replicate what would happen in a postmarket setting and in a premarket setting. But we do believe, given the data that we have from other countries, that the 15% that we saw here in the United States is -- we're confident that that's an achievable figure and possibly even an underestimate of where we may go, considering what we've seen in other countries. But Antonio can explain a little bit more.

MR. RAMAZZOTTI: If you take the totality of the studies that we have run in premarket in the U.S. and in other countries, and also the postmarket data that we have from the other countries, it is clear that there is a potential in the U.S. because our premarket communication studies show that there is an intention to use, which is, as we said, around 40%

for the intended audience.

The actual use study has indicated that that intention to use can translate into an actual use, and a proportion of the adult smokers who initiated to use IQOS HeatSticks can fully switch to it. Now, if we compare this to what we have seen internationally, we see a very similar pattern. In fact, if you look at the results of our actual use study, the U.S. is in the range of the results that we obtained in very similar premarket studies in the five markets where we have tested them.

And, in fact, if I can have Slide 2 up just to show that the range of all of our tests premarket, all of our test studies that we obtained in other markets, it ranges between 10% of the adult smokers switched exclusively or predominantly to IQOS in Switzerland, all the way to 38% in South Korea. And the 15% of U.S. is in this range.

Now, what we then observed postmarket is a very different picture, and it actually is more, in fact, a successful picture where the vast majority of the IQOS purchasers switched to it exclusively.

DR. THRASHER: So I understand, from this slide, that the eligibility criteria were even more stringent, and people

actually tried IQOS, and only those who indicated they were still interested in using were eligible. And so I assume that these numbers also kind of underestimate the actual switching.

MR. RAMAZZOTTI: I think, when we look at the studies in premarket, I think we should look at these studies as giving a magnitude of interest into the product, not a specific forecasting of what that will be. But yeah, so that's my answer.

DR. THRASHER: Then one final follow-up question, sorry. I mean, the Japan case study is certainly interesting. One of the differences that I see between Japan and the U.S. is around e-cigarettes. As I understand it, electronic cigarettes with nicotine are only available by prescription in Japan.

MR. RAMAZZOTTI: That's correct.

DR. THRASHER: And so I wonder if your modeling includes how it is that IQOS will be received in the context of a country like the U.S., where electronic cigarettes are already on the market and available as kind of a similar substitute for conventional cigarettes.

MR. RAMAZZOTTI: Yeah. And before asking Moira eventually to discuss about the modeling, I want just to give you a little perspective. In fact, you are correct. In Japan, electronic

cigarettes are only available, as you said, upon prescription.

However, in other countries where we are commercialized and where, in fact, I showed you results a second ago, there is a very different development of the cigarettes. In Italy, in Germany, in Switzerland, electronic cigarettes are available with nicotine. Also, in South Korea.

If I can have Slide 1 up. And this is the data coming from our postmarket consumer panels and with a different degree, but you can see that across all the markets, irrespective of the electronic cigarette development, the exclusive use is the most common behavior among the IQOS purchasers.

DR. THRASHER: And just to clarify, this is amongst people who purchased and then registered the product online and are now part of your consumer database?

MR. RAMAZZOTTI: That's correct.

DR. THRASHER: So they're more enthusiastic users.

MR. RAMAZZOTTI: Well, they purchased, indeed, and they're just -- to give you an example, the registration rate in Japan is about 70% of all the kits that we have sold in that market. So we source to include into this panel from 70% of the entire population who have purchased IQOS.

DR. HUANG: Next, we do have a question from Dr. Ossip on the phone.

DR. OSSIP: Yes, thank you.

This is a follow-up to Dr. King and Dr. Weitzman's questions, and perhaps someone else from earlier, regarding the potential impact on youth. You explained why you targeted specifically the adult sample and provided, I think, a clear representation of what you found. But two questions:

One is, in your markets where you have been -- you have had a presence for some period of time, like Japan, are there any sources of data someone is initiating? Are there similar kinds of surveillances that you are aware of or that could be accessed that could provide data on youth, similar to the kinds of things that Dr. Weitzman pointed out that we have in the U.S. and, in fact, query youth about use of other tobacco products?

And the second is, from your own dataset, you have the 18- to 25-year-old cohort, but do you have specific analyses on the 18-year-olds, how large is that sample? Is that something that could provide data, but did you assess that they're still in high school? Presumably, some of those would still be in high school. Given that most initiation in the U.S. occurs

during adolescence, whether adults are considering looking at messages and deciding if they plan to initiate may be different from looking at a population among whom the greatest amount of initiation is occurring.

So really the two questions. One is existing surveillance data in countries where you have been in the market for some period of time. And the second is, from your own dataset, do you have or can you provide analyses specifically on that 18-year-old group since that is the closest that you have to the -- at least the top end of the population in which most of the initiation is occurring?

DR. GILCHRIST: Okay, so I'll answer the first question, and then I'll ask Antonio to come and just address your second question regarding the specific 18-year-old cohort.

So as a matter of policy, we don't do studies in youth, whether it be in the United States or any of the countries where IQOS is currently on sale. It's just not something that we do. We're not aware of any published studies yet on initiation or potential initiation of IQOS among the youth age group.

Nevertheless, what I can tell you from our postmarket surveillance studies that are done in adult populations, we see

extremely low levels of initiation among nonsmokers, levels that really replicate what Antonio showed you earlier, in terms of interest among nonsmoker groups here in the United States. We're seeing very low -- very, very low -- single-digit figures in Japan since we've been doing postmarket monitoring there.

I understand that doesn't address specifically youth, but that's something that we're interested to talk with other parties about, about how we can gain data on youth without actually having to do that type of study ourself.

DR. OSSIP: Sorry, a quick follow-up on that. How do the initiation rates -- you say it's a very low level among adults. How does that compare to their initiation rates for combustible tobacco products?

DR. GILCHRIST: Much, much, much lower. Much lower. In fact, the vast majority of IQOS users in our postmarket surveillance in countries like Japan have initiated on combustible cigarettes. It's a very, very low percentage who've initiated using another product such as a heated tobacco product.

Antonio.

DR. HUANG: Is that related to price at all or --

DR. GILCHRIST: It's difficult to tell at this point in

time. I think the controls we've put in place to ensure that we're only selling to adults, adult smokers, are very important, so we're doing age verification, we're checking smoker status rigorously. So I think those things help. Price may play a role, but I think it's really too early for us to say at this point in time.

MR. RAMAZZOTTI: Just to answer the second question you had asked, whether we can break out the results within the LA to 25 for 18 or 19. Unfortunately, we cannot do it. I mean, we can physically do it, but it's such a small number that it would not allow us to take any firm conclusion because, as I was saying in my presentation this morning, we only recorded 12 LA to 25-year-old nonsmokers with intention, with positive intention to try, and only 4 with positive intention to use. So we wouldn't be able to draw any conclusion.

DR. HUANG: Dr. Blount.

DR. BLOUNT: I had several questions following up on the non-targeted differential screening for Dr. Peitsch. So related to that, do you have a list of the 53 chemicals that are found in higher concentrations in the IQOS submissions compared with cigarette smoke?

DR. PEITSCH: Yes, we do. Those constituents have been

listed in the December 8th amendment to the MRTP application, and a list of those constituents is available on the website pertaining to this meeting.

DR. BLOUNT: So additional to that question, did you have any efforts to measure exposure --

DR. HOLMAN: Ben, could I jump in real quick? It's me. Look to your left, look to your left.

(Laughter.)

DR. HOLMAN: That information is actually in your packages in the folder. If you look, the yellow-colored paper has the information you just asked about.

DR. BLOUNT: Thank you, Matt.

Was there any effort to measure exposure to those chemicals in users of the IQOS product as part of the different human studies?

DR. PEITSCH: No, there was not. The reason for this is that, for the human exposure studies, we used biomarkers of exposure for which there are validated methodologies that are available in third-party labs, you know, in CROs. Also, we did not know which compounds were up higher in the IQOS aerosol than in 3R4F before we actually started our clinical studies. Nevertheless, also important to realize that we are comparing

here with 3R4F, so we do not have a comparison with a marketed product, either U.S. or anywhere. Okay.

DR. BLOUNT: And then my final question you anticipated, and that was to put a toxicological perspective around those 53 different chemicals. You mentioned that they were below thresholds of toxicological concern. Could you elaborate on the techniques that you used to make such a comparison?

DR. PEITSCH: Yes, we have basically, for the four constituents that we looked at. For three of them there is -- there is actually exposure data in, for example, rat, long-term rat carcinogen. This is data, for instance. Can I have Slide 1 up? And so here we look at glycidol, 2-furanmethanol, 3-monochloro-1,2-propanediol, and furfural. There is evidence in the literature for three of them: the first, the second, and the last.

The work we've done here is that we calculated what would be the exposure for a person who uses 40 HeatSticks per day, and then from the animal studies, we looked at the exposure levels without tumors in vivo, which you can see in the third column. And from there, we actually calculated the delivered dose in milligrams per kilo per day. This particular dose, delivered dose, at the level at which there is no tumor, was

then transformed into the human equivalent concentration, again in microgram per kilo per day.

And then we looked at the ratio between basically using 40 HeatSticks per day, which would be two packs, and this human equivalent concentration, and that gives us ranges between 1 in 3 to 1 in 584. This is how we've done this evaluation.

DR. BLOUNT: Thank you.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes, thank you.

I'm going to go back to the data on switching. The table that you showed us shows basically that exclusive switching is about equivalent to recent cessation in the U.S., which is defined by people who have quit for, you know, at least 6 months or more.

And so I'm wondering, your data go up to 6 weeks. Did you consider longer-term data? Because with cigarette smoking, the reason why we go to looking at 6 months or longer is because of relapse rates. And so given that your exclusive user rate is equivalent to that of recent smoking cessation, did you consider collecting data more long term?

MR. RAMAZZOTTI: When we designed the actual use study, we assessed the -- and we thought very carefully to what would

have been the right length of product usage. We decided to use 6 weeks in order to give enough opportunities to the consumers who started using IQOS to decide whether to switch to it enough. This was also corroborated by our experience in the markets where we're already commercialized. That indicates that, in general, adult smokers who purchased IQOS can switch completely with between -- it takes between 2 to 3 weeks all the way up to 6 or 7, in some cases 9, at the beginning of the commercialization. So a 6-week duration allowed enough time for the participants to try, experiment, and establish a pattern of use of IQOS. We didn't go beyond the 6 weeks.

This said, when we look at our postmarket data, we do see across all the IQOS purchasers, and I would like to show again -- Slide 2 up, please -- that adult smokers can achieve full switching and can achieve it in substantial proportion as indicated by our postmarket panel service. And this full switching is achieved at the faster rate as the product stays on the market for longer.

DR. HUANG: Mitch, did you have something?

MR. ZELLER: Staying on the actual use study, can you put up Slide 85 because it is, I guess, fundamentally a definitional question of what you are calling switching. So

you are including exclusive and predominant use in your definition. And so my first question is -- and it's sort of a stratification question -- on the left side of this slide, in lumping those two together, you get a reduction in number of sticks per day, but this includes up to 30% cigarette use. So how does, whether it's red or orange, how does that vary as you go from 95% to 70% IQOS use?

MR. RAMAZZOTTI: Okay. I think, let me check with my team whether we can split the data, because on this slide they are put together and we will come back to you showing the data.

MR. ZELLER: And then I guess the bottom-line question is why are you including in the definition of switching up to 30% cigarette use?

MR. RAMAZZOTTI: Yeah, I can address that question. So in our way of defining the usage categories, in fact, what we have observed is that 95, I think, to 100% is clear. In fact, our postmarket results, when I showed the results of our postmarket panels and showing a 72% exclusive usage in Japan, defined with the same usage category -- 95, 100 -- when we go and really look for the people who only use HeatSticks and zero cigarettes, so 100%, that is 66% of that 72, 66 points of that 72. So it is very consistent, the pattern of usage evolution,

and adult smokers who use 95% IQOS most likely go to the 100% in slightly a few more weeks. Now, we have data; in fact, we have analyses like using mark of transition probability analysis that show that when it comes to predominant. Now, to address the second part of your question, adult smokers who use IQOS predominantly have a much higher probability to become exclusive users than the opposite. Can I have Slide 2 up, please?

That is the mark of transition metric of probability established upon the data we have in the postmarket consumer panel in Japan, and it shows that if you take exclusive users who use IQOS at 95 to 100% in the first 3 weeks, 80% or more of them remain so, looking at Week 10 to 12. And those who were using predominantly IQOS in Week 1 through 3, at Week 12, 63 -- they have a 63% probability, in fact, to move up to exclusive use, and only 24% to remain so, or 12% to become -- in other words, these data indicate that the reason of a patient here, which is transitional, that allow consumers -- adult smokers to fully switch.

MR. ZELLER: Okay, just then one follow-up question. Are you asking this Committee, then, to make an assumption, when you say switching includes both exclusive and predominant, that

based upon non-U.S. postmarketing experience and data, that there's an assumption that there's going to be a transition from predominant to exclusive in your definition of switching in the United States?

MR. RAMAZZOTTI: I'm not asking to make that assumption. I'm providing these data to explain why we categorized the IQOS users in the way that we discussed. So the exclusive, 95 to 100, and predominant, 70% and above.

DR. HUANG: Dr. Rees.

DR. REES: This question is for Dr. Gilchrist. The simulation model is very interesting and the conclusion that potentially, in a best-case scenario, 90,000 lives could be saved. I believe that's over 10 years?

DR. GILCHRIST: That was over 20 years.

DR. REES: Over 20 years.

DR. GILCHRIST: Um-hum.

DR. REES: So that's four and a half thousand lives saved per year, offset against 480,000 lives estimated lost to tobacco annually. I'm interested in less optimistic scenarios, and I think, as you sort of wrapped up, you said -- I think your phrase was literally millions of people would have to commence smoking to offset the gains that might be observed

under this best-case scenario. I'm interested in your data that suggests that up to 8% using the Surgeon General's warning, up to 8% of former smokers expressed an interest in using IQOS. Would former smokers who begin using IQOS be offset against the benefits that you'll observe? I'm also interested in whether youth has been factored into this model and whether this model factors in the real-life scenario of the proliferation of e-cigarettes.

DR. GILCHRIST: So Gizelle Baker will answer that question. She's our expert in epidemiological modeling.

Gizelle.

DR. BAKER: Hello. Gizelle Baker, health outcomes and biostatistics. In this model we did account for relapse rates, and we did allow for initiation rates. But based on the PBA data, the way we looked at it is that they weren't going to materially change the initiation or relapse rate.

It was going to distribute what they relapsed to or what they initiated with. So we did include those into the model. As for youth, we did include -- the model started at age 10, of which we didn't have any smokers, and then probabilities were assigned starting with the 10 to 14 age to be able to replicate what we saw and were able to match to the U.S. smoking

statistics where the majority of initiation happened in youth. So that was incorporated into the model as well.

DR. REES: So what does your worst-case scenario look like?

DR. BAKER: Well, when we were looking at it, we looked at the 15% IQOS use plus 2% dual use. We ran multiple simulations, and we published a paper with hundreds of different scenarios. But in the dossier, we included scenarios where we actually had -- we had no impact on cessation. We also ran it where we had an impact on cessation and with initiation, as well as doubling initiation rates in these types of scenarios to understand.

In the model, we were able to see that even with some of the worst-case scenarios where we still had a reduction in the total number of smokers in the U.S., we were looking at 30,000 lives over the 20-year period.

But we have to remember that the initiation isn't 15% on Day 1; it was 15% over time, starting to use the product, and the length of time that they're using the product affects the reduction in risk. So the reduction of risk doesn't go down on Day 1 when you switch to IQOS. For things like lung cancer, we expected that the half-life of excess risk was somewhere around

10 years. So they have to convert to IQOS for a long period of time before the full benefits of the reduction in risk come into play.

DR. REES: Was the changing environment of e-cigarette use factored into your model?

DR. BAKER: It was not in the model as it was when we submitted it, because when we started the modeling project, e-cigarette use was not that large in the U.S. We are working to increase the model so it will be able to look at that as well, but we did run scenarios where we lumped e-cigarettes into the IQOS use. So we had a larger number in the reduced risk category, but we didn't differentiate the risk because there was a lack of data on it between IQOS and e-cigarettes.

DR. HUANG: Dr. Mermelstein.

DR. MERMELSTEIN: Let's switch gears just a little bit because I'm curious about some of your marketing approaches and if you're having retail shops and how those influence the overall perceptions and acceptability. And then also, as part of this, do you anticipate your sales reps, who are in there and who are basically training people on how to use the device, providing cessation messages as well?

MS. KNAKMUHS: Certainly. So let me first take the retail

question and then talk a little bit about what we kind of call our IQOS experts.

We're looking at -- if we could show Slide 2, please -- a number of different approaches on how to build awareness and define the right way to have trial for consumers, and one of the ways that we're looking at doing that are called IQOS-branded stores. And that would be an opportunity for -- let me actually show you one more slide as well. Slide 1, please. Making sure we're having the right consumers coming into the store. If you walk into an IQOS store, someone would have to show their identity, government ID, to confirm that they're an adult before they'd be allowed in the store.

Once they're in the store, if they want to do a guided trial, they'd have to confirm that they're a smoker, and then when they actually purchase the device, they can register for additional support.

But we're looking at using that store as a way to build awareness about what IQOS is for the consumer, help them provide support: How do I clean this thing, how do I turn it on, turn it off, what do these lights mean? And those are some of the ways that we're looking at using standalone stores.

On your second question about what sort of messaging, I

think it was specifically a question that was around cessation advice, our IQOS experts will provide -- we have comprehensive training that we'll put folks through what is allowed to be said, what is not allowed to be said. They'll go through training, there will be independent auditing.

If we see any problems, there will be remediation, but they will not provide any specific cessation advice. If someone comes in a store and says, hey, I'm looking to quit smoking, I want IQOS, we'll be very clear that they will say this is not a cessation device.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Thanks.

I'm wondering, either based on any work you've done in development or experience in the field, what the boundaries are around potential misuse of the device and/or the HeatSticks. So, for example, what happens if a consumer sticks a standard cigarette in this?

DR. GILCHRIST: Um-hum.

DR. O'CONNOR: What if a consumer lights a HeatStick? Are there ways or are there potential ways or have you explored potential ways that the actual holder can -- the safeguards on the holder can be defeated?

DR. GILCHRIST: Yes, we have looked at this quite extensively. With regard to -- okay, there's a few conditions of use suggested there. So misuse using a conventional -- a regular cigarette in the device. The holder, actually, and the HeatStick have a very specific diameter which is quite uncommon in the conventional cigarette portfolio of products that are available. Number one, it would be quite difficult.

It is possible, however, to find one that will be able to fit in. But when you actually try to use it, because the tobacco has not been processed in a way that we do to ensure that it performs when you heat it rather than burning it, there would be absolutely almost no aerosol to be able to use. So the likelihood of misuse in that way is very, very low because it's simply the cigarette -- the tobacco in a regular cigarette just will not perform at low temperatures.

Then you asked about whether somebody, if they lit the HeatStick -- I don't know if you noticed when it was passed around, the HeatSticks are very small. So, number one, it's actually very difficult and a little bit scary to try and do that, but we have tested whether it's possible; it is. The smoker would get perhaps four to five puffs, something like that, so a short -- a smaller number of puffs. But we did test

some chemistry of the smoke, as I mentioned earlier in the question from Dr. Rees, and we see that the levels of harmful chemicals are roughly the same as you would find in a combustible cigarette and certainly nothing that brings concern. So we have looked at those.

And then I think the last thing was is there a way somebody could override the safety mechanisms in the device? Now, of course, we can't ever rule that out, but we have worked extremely hard to prevent that the software can be hacked. So we've done work with outside specialists to help us ensure that we have the software properly encrypted.

So there's no way that we are aware of that somebody could actually physically manipulate that. But, of course, we've very aware that we have to keep track with what can be done in that sort of area, but we certainly have looked at that.

DR. HUANG: Actually, as a follow-up, Dr. Rees, did you get satisfaction in your earlier question regarding, sort of, the combustion temperature for these products?

DR. REES: Well, what I was getting at is the combustion temperature is substantially -- for the HeatStick, it's substantially lower than that for a cigarette. Then, as you approach the switch-off point, you're getting close to the

point of combustion for a HeatStick. And I think that's interesting because you've only described combustion temperature in terms of a conventional cigarette, but that's irrelevant in this case. I'm more interested in the combustion temperature of a HeatStick, and you didn't give us that number.

DR. GILCHRIST: Okay. So combustion processes can start at around -- above 400 degrees centigrade.

DR. REES: Can I interrupt? Combustion processes for a conventional cigarette, yes, we know that, we understand that. But what is it for a HeatStick?

DR. GILCHRIST: I will ask my colleague Maurice Smith. He's our expert --

DR. McKINNEY: Can I ask a clarifying -- are you asking at what temperature do you get an aerosol? Is that what you're asking?

DR. REES: I'm working on the assumption that as we get closer to the point of combustion, we're getting a different mix of chemicals in the emission, and I'm wondering how close we're getting to the point of combustion with a HeatStick.

DR. SMITH: This is Maurice Smith, regulatory and scientific affairs.

So when you begin to heat the tobacco in IQOS, you get

evaporation, you lose water, you generate volatiles, so the glycerol is then also produced into the vapor, and that cools and forms an aerosol. So the temperature is limited, so it can't exceed 350 degrees because that's the set point for the device. So there's no combustion in IQOS; it doesn't approach the combustion temperature.

As you know, a conventional cigarette operates at between 600 and 800 degrees, depending on whether you're taking a puff or not, and we're only going up to 350 degrees. So the chemistry we've seen from the diagram that Manuel showed, what's produced is very different, so you get an aerosol and not smoke. I'm not sure if that's answering your question.

DR. REES: I'm surprised that you cannot tell me the temperature of combustion of the HeatStick.

DR. SMITH: The temperature of combustion of a HeatStick would be very similar to the temperature of combustion of a conventional cigarette because it's the same tobacco; it's compounded differently, but it would start to combust at a very similar temperature to --

DR. REES: Well, thank you, but the reason I pushed this is because it's been explained to us that it's quite different to a conventional tobacco blend.

DR. SMITH: It's different in formulation because then you need to get a uniform heating process. So that, then, is more explained. You get that reproducibility in terms of the aerosol generation between puffs and between sticks. But no, it's a different formulation, but the way it behaves, it's still a tobacco biomass which would behave as tobacco.

DR. HUANG: Okay, Dr. Blount.

DR. BLOUNT: So perhaps a clarification of that. Technically, it would be have you performed a flashpoint test with the filler in the HeatSticks as compared with conventional cigarette filler and compared those temperatures?

DR. SMITH: Yes. Well, we haven't done a flashpoint. I mean, we've taken out the plug and we've done -- metric analysis where you can see what's generated over a temperature run up to 800 degrees, and what we clearly see is you can also run that in air or in nitrogen, so when combustion is excluded.

So you see some peaks, as I explained before, and you get water loss and loss of volatiles, and that occurs up to 350 degrees. When you get above that, at 420 degrees, if there's oxygen present, you start to see the products of pyrolysis and combustion. We don't see that in our IQOS product because we're operating below that 400-420 degree threshold.

DR. HUANG: Okay, Dr. Giovino.

DR. GIOVINO: Oh. Well, thank you. I have many questions, but I'll only ask a couple and then give other people a chance. The presentation on risk of relapse in former smokers looked at all former smokers. Now, when I quit smoking, the real -- I'm 35 years past cigarettes, and I agree totally with what your people are telling you, but I relapsed a couple of times because I thought light cigarettes were safer, and we know now that that's not true. But my real question for you is did you stratify the intention to try based on duration of abstinence among the former smokers?

MR. RAMAZZOTTI: Yes, we did. In fact, we included former smokers who had been abstinent between 30 days and 1 year. Call it for convention, always we call them short-term quitters. And we have also former smokers who have been abstinent for more than 1 year, so that we call the long-term smokers.

We didn't see a lot of difference between the two. In fact, we did see some -- I think the ITU, the intention to use, was higher among the shorter-term quitters than among longer-term quitters. In any case, I think postmarket results are best designed to give real-world data on this issue, but these

are the data that we have --

DR. GIOVINO: Thank you.

MR. RAMAZZOTTI: -- in our studies.

DR. GIOVINO: Thank you. Actually, while you're up there, is it possible to see the data on a hundred percent exclusive use? I've been in tobacco cessation for a long time and, you know, one cigarette often prompts a relapse. You know, I understand -- and we still haven't answered Dr. Wanke's question about what do these markers look like for dual users. But it would help me understand really who is going to a hundred percent, and I would like to understand that before I finish processing all of this. So could that data be provided?

MR. RAMAZZOTTI: Yes, we do have data from the actual use study among those who completely switched, so at zero cigarette level. I think we should have a slide on that or data on that. I can definitely reconfirm it after one of the breaks, but going by memory, it is 8%, as defined 95 to 100.

DR. GIOVINO: Is this Japan, or is this the United States? What is this?

MR. RAMAZZOTTI: That's United States actual use study.

DR. GIOVINO: United States.

MR. RAMAZZOTTI: I think the number is 5.8% at the end of

the 6-week were 100% IQOS use, but I would want to double-check this number and come back to you after one of the breaks.

DR. GIOVINO: And you're saying 5.6% of the total sample, not 5.6% of the 8%, right?

MR. RAMAZZOTTI: No, the 5.6% --

DR. GIOVINO: Okay.

MR. RAMAZZOTTI: -- of those sampled, but let me double-check this number and come back to you after one of the breaks.

DR. GIOVINO: And then I think it was Japan. You alluded that over time there's proportionally more exclusive users, like, you know, 95 to 100%.

MR. RAMAZZOTTI: That's correct.

DR. GIOVINO: Could you also show the data for a hundred percent exclusive use for Japan?

MR. RAMAZZOTTI: Yes, we can. Let me check with my team if it is possible. I quoted one number that I did have in my memory, and I can provide you, in fact, with the data. But out of that 72% that we showed as exclusive use of 95 to 100%, I have vividly in my memory, it is 66. So 66 points of those 72 is 100% IQOS, zero cigarettes.

DR. GIOVINO: And did it increase over time, do you

recall? I mean, I'm asking a lot.

MR. RAMAZZOTTI: Yeah. No, no, no. It's very relevant questions. And indeed, as we look at the progression over time, that proportion of complete switching at 100% also increases, and that's very consistent with the different behavior of the different cohort of purchasers.

DR. GIOVINO: Thank you.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Following up on Dr. Giovino's question is from a global perspective, who are the people who are most likely to be transitioning to exclusive use? Are they older smokers? Are they ones who have stronger intentions to quit? Have you looked at -- and this really hasn't come up yet, but have you looked at sex differences? Have you looked at racial/ethnicity differences? So I'm curious as to who this group of smokers is to whom IQOS is particularly appealing.

MR. RAMAZZOTTI: Yeah. In the U.S. actual use study, the typical switcher is above 25 years of age consuming, in general, between 1 and 10 cigarettes a day and -- yeah, that's basically the characteristics that I can remember.

Now, internationally, what we see across IQOS purchasers is that the typical profile of the exclusive user is over index

in the 30 to 49 years old. This is across all markets when compared to cigarette smokers, and we see lower proportion of usage among LA to 24. That's also internationally.

DR. HUANG: I think Dr. Giovino has a follow-up here.

DR. GIOVINO: Oh.

MR. RAMAZZOTTI: And excuse me, I just forgot.

DR. GIOVINO: Sure.

MR. RAMAZZOTTI: And typically more male smokers.

DR. GIOVINO: I'm really curious about level of addiction. Have you looked at level of addiction to cigarettes as a predictor of quitting? Is that factor relevant to your thinking? This is more curiosity. I mean, is there differential switching based on level of addiction?

MR. RAMAZZOTTI: We haven't looked at level of addiction and to establish that proportion that you asked for in our studies in the U.S. So no, we didn't, but --

DR. GILCHRIST: I would just ask Gizelle to come and discuss whether we have that sort of information from our clinical studies, though, because there we did look at potential factors that could give us a measure of addiction.

DR. BAKER: Hello. In the clinical studies, we had 80 people on the IQOS arm and 40 in the CC arm, and obviously,

because here they're randomized to the product, it's not necessarily the addiction level that's going to be predictive of the outcome. But what we did notice when it came to the addiction is that when we use the Fagerstrom score, we actually saw more downward progression in the IQOS arm after the complete study.

DR. WEITZMAN: What does that mean?

DR. BAKER: In the IQOS arm, we had about 23% of the people who were rated, according to the Fagerstrom, as severe transition down to moderate, where it was about 18% in the conventional arm, and both had about 4% go up. But we can't really use this to predict into that because of the randomization.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: So I'm interested for the sample, I'm interested for your sample how participants were chosen, what the inclusion and exclusion criteria were, what sorts of incentives were given to patients. I'm also interested -- you began by saying that you've published in a fair number of papers. It would be very useful to know what journals those publications were in.

And then to build on Dr. Fagan's question, we talked about

menthol. We didn't talk about harm or effect of menthol, and I do believe you have other flavors as well. Do we have any data about what happens biologically when you have different flavoring?

DR. GILCHRIST: Okay. So maybe I'll start with how the subjects were chosen and brought into the study. So, of course, we have two types of studies. We have the perception/behavior --

DR. WEITZMAN: Right.

DR. GILCHRIST: -- assessment studies, which I'll ask Antonio to address first, and then we have the clinical studies, which I'll ask Gizelle to come up and answer. And then after that, she can address the question about menthol. Does that sound okay?

DR. WEITZMAN: Menthol and other flavors.

DR. GILCHRIST: And other flavors, yes.

DR. WEITZMAN: Thank you so much.

DR. GILCHRIST: Of course, here in the United States, flavored products would not be allowed because IQOS is classified as a cigarette. So the regular and the menthol variants would be the only ones that would be allowed for sale here.

MR. RAMAZZOTTI: Yeah. So in terms of the recruitment, we have used a different set of agencies who have, in fact, performed different ways of recruiting the consumers. All participants were reimbursed adequately for their time and effort in participation.

DR. WEITZMAN: What does that mean?

MR. RAMAZZOTTI: Excuse me?

DR. WEITZMAN: What does adequately mean?

MR. RAMAZZOTTI: I'm coming to that. In fact, just to give you an example, the participants that received -- in the actual use study was where we reimbursed monetarily. Consumers we rewarded -- sorry, they received a maximum of $440 at the end of the study, depending on their participation, their completion of all the tasks, including recording into the electronic diary, returning the device and the unused product, and the reimbursement was not linked at all to the consumption of HeatSticks, of course. And so this, in general, taken all together, is about $6 per week of participation, which is reasonably normal in the U.S.

DR. HUANG: Dr. Wanke.

Oh, did you have more?

DR. BAKER: Did you want the information for the clinical

studies as well?

DR. HUANG: Sorry.

DR. BAKER: Okay. So in the clinical studies, we identified adult smokers. We looked for 3 years of exposure to ensure that they had levels of exposure so we could measure reductions. We looked for healthy volunteers, so we had assessments using standard methods. So we had clinical -- clinical labs were done and safety labs were done, ECGs, spirometry, and these types of things, to ensure that we had healthy adults in this population. We also had quotas so we ensured balance between males and females, as well as based on amount of consumption of cigarettes at baseline. And that's how we enrolled them. We used large CROs using standard methodology for -- that's commonly used in the pharma industry, so we had an ICF.

It was also vetted to the IRB, and they were compensated based on the amount of effort it took. And we have to remember, in the clinical studies the amount of effort was far exceeding what we saw in the PBA studies because they were on site for 2 or 3 days at baseline and they had to remain on site and then, as well, when they came back at Days 30, 60, and 90.

But they were not discounted even if they did not use the

IQOS. We kept everybody in the study so that the reimbursement was equal and not influenced by product of use.

DR. WEITZMAN: I apologize, but I don't think I was clear in my question. It really had to do with your animal model studies where you looked at inflammatory markers and changes in predictors of cardiovascular disease and endothelial changes, lung changes. Did you look specifically at those who received menthol?

DR. GILCHRIST: Oh, sorry. Okay, so that is Gizelle.

DR. WEITZMAN: I think that was my fault.

DR. GILCHRIST: That was a clinical study. Apologies, that was a clinical study, not an animal study, where we looked at the different clinical risk markers or biomarkers of potential harm, as the FDA referred to them in their briefing book. So that's Gizelle. And we did look at menthol in those studies.

DR. BAKER: So in the clinical study where we had reductions in exposure, we also measured a set of clinical risk endpoints that were known to be associated with smoking and reverse upon cessation. And in that study we had, the Fresh Menthol variant was used. So all of the data showing the reductions in exposure is linked in that study to menthol. Did

you want me to bring the reductions in exposure up again to look at?

DR. WEITZMAN: No, I trust you.

DR. BAKER: Okay.

DR. HUANG: Dr. Fagan.

DR. FAGAN: I just have a follow-up question here with regard to the clinical studies. So you said that you looked at menthol with regard to the outcomes. Some of the studies, including like the multi-ethnic cohort study, show that African Americans in particular tend to -- you find more tobacco exposures in them when you're looking at urine or blood samples, for example.

And so what I would like to know is, in the sample that you used specifically to menthol and to the regular, you know, what was the percentage of African Americans included, and did the outcomes look different for that group? Because other studies related to cigarette smoking shows that those particular biomarkers are higher in this group.

DR. GILCHRIST: Okay, so we're in a position to be able to directly compare both the regular and the menthol product for the first 5 days of confinement, and there we didn't see any difference; the addition of menthol didn't provide any

difference between the biomarkers of exposure during that time period. And then for the 90-day study, both of those studies, one in the Japan and the U.S., used a menthol product. But the data that we have in hand leads us to conclude that menthol did not increase any of the exposures to the biomarkers that we measured. And in terms of participation of African Americans within the study, Gizelle is the best person to answer that.

DR. BAKER: So we only had African Americans in the U.S. study, obviously, and there we had about 39% or just over 39% of the population was African American.

DR. FAGAN: And -- go ahead.

DR. BAKER: What we do see is that they were slightly higher with the exposure, dependent on the number of cigarettes obviously. And with the small sample size, once you start breaking it down to number of cigarettes per day and then by race and then by sex, we get two very small samples. But we did look, just to ensure, at change from baseline where it starts with the baseline compared to where they ended up, and we didn't see any difference by race.

DR. FAGAN: So you're saying that 39% of the sample was African American. Are these all menthol smokers?

DR. BAKER: It was a menthol study conducted in the U.S.,

so yes, all of them were menthol smokers.

DR. FAGAN: Okay. And then you're saying that the outcomes related to the biomarkers were slightly higher among the African American menthol smokers compared to whom?

DR. BAKER: At baseline they were slightly higher, but the change from baseline was very similar, independent of race.

DR. FAGAN: Okay.

DR. BAKER: So at baseline they were all using the combustible cigarettes, and we did see, but in small -- because it's hard to really make a conclusion on that because the number one driver for exposure level at baseline is number of cigarettes they were smoking, and then when you break that down across them, there's not very many people. So I can't conclude that they were statistically higher, but numerically, they were slightly higher at baseline than in the Caucasian population or the population as a whole.

DR. FAGAN: So right now you're talking -- you don't have sufficient sample, that's what I'm hearing from you, in order to --

DR. BAKER: I don't have sufficient sample to make a statistical conclusion.

DR. FAGAN: Okay.

DR. BAKER: But what we did see is that the change from baseline in that population, and so therefore the reduction in exposure or the percentage of reduction in exposure was very similar between races.

DR. FAGAN: Thank you.

DR. HUANG: Dr. Wanke.

DR. WANKE: Thank you.

This is a follow-up to Dr. Giovino's point about the complete switching. When we talk about exclusive use including 95 to 100%, I want to have a practical understanding of that. Would I be correct in saying that would include someone who's a pack-a-day smoker smoking a cigarette a day? If I think about 100 cigarettes, 5 out of 100 cigarettes are still smoked, 95 are switched over to IQOS, so that would be equivalent to a pack-a-day smoker smoking a cigarette a day.

DR. GILCHRIST: Yes.

DR. WANKE: Does that sound correct?

DR. GILCHRIST: Yes.

DR. WANKE: So then this is also going to follow up to the point that Dr. Zeller made, that not only when we're combining exclusive and predominant use categories, even when we're considering just an exclusive use category that includes dual

users who smoke up to a cigarette a day, if they're -- let's say for a pack-a-day user. So I echo the point that I'd like to see the data for --

DR. GILCHRIST: Yeah.

DR. WANKE: -- true 100 percent use. So given that -- and then I want to return to the idea of the studies that were showing us the reduced exposure data in humans, because I want to know what kind of definition you have both for IQOS use and for smoking abstinence.

So would someone who is an abstinent smoker, since that's the comparison group, somebody who switched to no product, also include those users who might smoke, say -- who may have some minimal use? It isn't 100 percent use; it's perhaps 95% use.

DR. GILCHRIST: So in the confinement period of our reduced exposure studies obviously, we monitored that so people that were in the abstinence arm had no product whatsoever, and we knew that they didn't use any product. But over time, in the 90-day study, we also had other measures that we used to be able to determine whether people had actually switched either to IQOS or had abstained. Gizelle is the best person to give you details.

DR. BAKER: Okay. So in the study we used, obviously

multiple different populations, and we analyzed them all and presented them in the dossier. Our primary analysis was what we called the per-protocol population, where we required them to use at least 95% IQOS during the entire exposure period, as well as to have used no more than two in any given day during the period that we were analyzing them.

So it was a little more strict, so you couldn't have one a day every day because we had also on that an average of 0.5 a day over the course of the study. So that was a much -- a slightly elevated definition.

But we also had in there a compliant use population. So that was the one where we used the restriction that it had to be all IQOS, and then we did similar things with the smoking abstinence. So we had a limitation on the number of cigarettes per day, and we also had an average per day during the period, but we also had a compliant population that we analyzed.

And if you would like, I can throw up one slide, like Slide 3. And here you see the difference in the populations. So the blue is for everybody who was compliant, and the red in the middle is the per protocol, and then what you see in green is the full analysis set. And so what you see is the reductions compared to continued smoking are very similar,

independent of the population.

DR. WANKE: So when you mean compliant, you mean compliant with IQOS or compliant with abstinence?

DR. BAKER: In this one, we're looking at IQOS compared to continuing smoking and this is -- so therefore only in the IQOS arm.

DR. WANKE: Okay. And so just to make sure that I understand that, that you -- in the exposure studies you had a more strict definition of switching to IQOS than the 95%?

DR. BAKER: Yes.

DR. WANKE: So then in the modeling studies where you're using this data and extrapolating, I'm wondering if you're doing apples to apples. Are you looking at using this exposure study but yet using the definition of the proportion of people who are exclusive users? That's the more generous definition.

DR. BAKER: So in the modeling, when we looked at the transition rates, we were targeting a 15% exclusive use over a 10-year period. So we were doing the apples to apples, we're looking at what we can expect when people actually switch, and then we did the assumption that dual use contained everything in between.

DR. WANKE: Okay. And then the one final is just to make

sure that I understand the abstinence criteria. When you were looking -- comparing the IQOS condition to those that are abstainers, were they biochemically verified that they were abstainers? Was there allowing for some cigarette use still to be considered within that category of smoking abstinence?

DR. BAKER: So, yes, we did have different tasks for compliance, and obviously, in confinement, where the product was out, handed out stick by stick, people in the abstinence arm obviously didn't get access to any of the products. And then there was also separate smoking rooms so there was no cross-contamination. In the ambulatory period, we did allow for a little bit of dual use, which was again using the less than two sticks in any given day and on average less than 0.5 per day. But we also did the analysis on that as well, using the 100% smoking abstinent group. But the numbers in the U.S. were very small.

DR. WANKE: Okay.

DR. HUANG: So I'm getting the word, we do need to eat lunch soon. We'll do two questions.

Dr. Bierut.

DR. BIERUT: Yes, thank you.

I have a question about the population modeling. And so

my understanding is that the population modeling was from 1990 to 2010, and there were 90,000 lives saved over that -- would've been saved by that 20 -- over that 20-year period. We're really in 2018 and not 1990 to 2010. And I understand that you would validate your models and you have real data that you could use to do that.

Have you extended your modeling out to the current time period? Because with our decreasing population prevalence of smoking, I would assume that the number of lives saved would be decreasing.

DR. BAKER: So we are in the process of extending the model into predictive modeling, but obviously when we start doing that, there are many other factors that we have to take into account. And what we did and are working on is a forecasting model where we look at how trends and different other characteristics that are known to impact mortality from disease, such as GDP within the country, inflation rates, and diet, and all of these other things are changing because these can impact the overall smoking-attributable mortality.

What we do see when we look at this, and obviously we aren't to the spot where we have that completely validated and ready to share in the forward looking, is similar numbers of

saved -- of reductions in smoking-attributed mortality in our first runs, which we're still refining. But a lot of this has to do with the fact that although prevalence is decreasing, the number of smokers is not significantly going down, so therefore there's the same number at risk for smoking-attributable mortality.

DR. BIERUT: Okay, thank you. And I have one other kind of minor question about what the word means. When I see the word "significantly," you know, statistically we have a whole idea of what that means, and that was in your warning, potential warnings. What do you guys mean when it's like you were saying harm was significantly reduced? What does that word mean?

DR. GILCHRIST: Do you want to take it from a consumer perspective? Yeah, Antonio will address from a consumer perspective.

MR. RAMAZZOTTI: So as you mentioned, in our Claim Number 3, we are using the word "significantly" for reduction of exposure, of the body exposure. Now, we have done a lot of studies, formative and confirmatory, in order to come up with the wording that we are using.

So in our qualitative studies, when we expose the consumer

to that claim, they -- most of them assume that it means that the exposure is reduced by 50% or more. So that's how they understand the word "significantly" from the consumer standpoint.

DR. BIERUT: And is that what you were trying to tell them?

MR. RAMAZZOTTI: Well, what we're trying to tell them is that there is a reduced exposure, and when it comes to -- if you look at the results of our comprehension, the majority of the consumers understand that the reduction of harmful and potentially harmful chemicals is significant.

DR. BIERUT: Meaning 50% or more?

MR. RAMAZZOTTI: They could interpret that it's 50% or more, as we heard from that. And since I'm here, can I just confirm, Mr. Chairman, the number that Dr. Giovino and Dr. Wanke were asking for, the complete switching 100 percent usage in the actual use study in the U.S.? In fact, it's 5.8% of the total sample of the population in the study. So thank you very much.

DR. HUANG: Our last question before lunch is Dr. Rees.

DR. REES: I'll try and make this very quick. We saw greater rates of switching among the Japanese sample, which

approached something like 30% complete and incomplete switching compared with about half that in the U.S. Can that be explained by the fact that Japanese smokers are accustomed to a different tobacco blend accompanied with a charcoal filter? In other words, they smoke -- they're used to smoking very different products from smokers in the United States. That's the first part of my question.

DR. GILCHRIST: That could be one explanation, and I think there are multiple things that are cultural differences obviously that play a role. So the pressure on Japanese smokers to be socially polite and not bothering others is an important factor, we know, in Japan, but there are multiple factors that could play a role.

DR. REES: Thanks, that's helpful. I think in past decades we've seen products that are similar, at least superficially, to this, to IQOS. Accord comes to mind. Heatbar is another example. And other reduced emission products, for example, Marlboro UltraSmooth, haven't gained traction with U.S. smokers.

And I think you mentioned earlier in your comments that smokers did describe differences in the sensory qualities of IQOS compared to their usual brand of cigarette. I'm

interested in understanding that a little more because if the difference is great enough, I imagine that the product won't be very commercially successful.

I'm also interested whether -- if you market this product under the brand Marlboro, there might be some carryover effect that may lead smokers of conventional Marlboro products to assume that their conventional product is also safer.

DR. GILCHRIST: Okay.

DR. REES: So just to summarize my point, if this is a product that yields very little in terms of commercial impact yet stays in the market and has the influence on smokers of conventional products to lower their perception of the risk of that product because it's being marketed as a Marlboro product, that may raise concerns.

DR. GILCHRIST: So perhaps I'll take that last question first. In fact, we're seeing in Japan the exact opposite happening. So we're seeing our Marlboro share declining in the same way as the overall market is declining in Japan and by 18% in the last year. So I think that's very encouraging. There seems to be no detectable spillover effect into different perceptions about the Marlboro brand in terms of purchase at least.

Now, if I go back to the Heatbar question, yes, Heatbar was our product, and we did try and launch it in several countries, and it was -- commercially, it was not successful. However, we took tremendous learnings from that failure. We worked extremely hard on making the device become much more ergonomic, so easy for a consumer to use in the way that Heatbar wasn't. So it was a huge, clunky thing that was really not acceptable to consumers. We also worked on lowering the temperature to ensure that we could minimize, to the extent possible, delivery of harmful and potentially harmful chemicals.

And then lastly, we worked extremely hard on the taste and flavor through understanding better which tobacco blends worked at those lower temperatures and so that we could provide a taste and flavor to smokers that would be much closer to what they were used to from combustible cigarettes.

And we believe we have achieved a real step change compared to what was on offer back in the 1990s and early 2000s with Heatbar, and we certainly see from our results in other countries that IQOS is a product that smokers can switch to and switch to in large numbers, and we also see that they can stay with it and not go back to combustible cigarettes.

DR. REES: Thank you.

DR. HUANG: All right, thank you. And I apologize for going over significantly, but I think there's obviously very much important questioning that needs to occur during this section.

We are going to break for lunch. We do -- and we'll return with the FDA presentations, but we would -- I think there is still some interest in having an opportunity for additional questioning after that regarding this, so we'll plan on that also.

And so let's see, please -- we'll probably take a 30-minute break for lunch. Committee members, again, please remember there will be no discussion of the meeting topic during lunch either amongst yourselves, with the press, or with any members of the audience. And also that members can go to the front of the line at the kiosk to facilitate this.

(Laughter.)

DR. HUANG: So we will, again, reconvene in 30 minutes.

(Whereupon, at 12:42 p.m., a lunch recess was taken.)

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

(1:20 p.m.)

DR. HUANG: So we're going to go back to the -- now the FDA presentations, and so we'll start out with Dr. Zuck.

(Pause.)

DR. ZUCK: Good afternoon, my name is Dr. Karina Zuck, a chemist in the Office of Science in the Center for Tobacco Products of the FDA. I will present the evaluation of the product chemistry in regards to the health risk of the IQOS use. Before I start, I have the following disclaimer.

I will present first a summary of the evidence from the Applicant. This summary includes the description of the product, the composition of the HeatSticks, and then testing data. After that, I will focus on the FDA preliminary assessment from a chemistry perspective. This section will include an overview of the independent testing performed and also a review of the published literature.

The Applicant describes the IQOS tobacco heating system as a heat-not-burn tobacco product consisting of three main components: the IQOS HeatSticks, which is a filtered, non-combusted cigarette designed to function with the IQOS holder to produce an aerosol when the tobacco blend is heated;

the IQOS holder in which the HeatStick is inserted and keeps the tobacco material; and the IQOS charger, which is used to recharge the holder after each use.

I will focus now on the HeatSticks ingredients.

The tobacco blend in the HeatSticks include only reconstituted tobacco. This is in contrast to combusted cigarettes, which typically include tobacco leaves, for example, flue cured, burley, or oriental tobacco leaf, expanded tobacco, and reconstituted tobacco. In addition to tobacco, the main ingredients included in the HeatSticks are the humectants glycerol and propylene glycol.

To characterize the product, the Applicant submitted data from different analytical studies. This slide summarizes the most relevant studies from the chemistry perspective that the Applicant submitted. For the sake of time, I will present the results reported only in two of these studies.

First, I will present a study labeled by the Applicant PMI-58, which includes yields of glycerol, nicotine, tar, total particulate matter, water, and 54 HPHCs obtained under modified Canadian intense smoking regimen.

And second, I will present the results from a non-targeted differential screening study which includes data for

constituents present in the aerosol of the IQOS at higher concentrations than in the smoke of the Kentucky reference cigarette 3R4F. The reference cigarette, 3R4F, is made for research purposes only and is not for human use.

In these two studies that I mentioned, the Applicant compared the data obtained for the HeatSticks with data from the reference cigarette 3R4F.

In addition, the Applicant submitted two other studies. Tar, nicotine, and carbon monoxide yields using ISO smoking regimen and a dataset labeled by the Applicant, FDA 18+6, which includes the yields of 18 HPHCs in aerosol obtained under ISO and modified Canadian intense smoking regimen and 6 HPHCs in the tobacco filler.

As I already mentioned, for the sake of time, I will present the results on the first two studies. Let's focus first on the PMI-58 data.

The PMI-58 data includes yields of 54 HPHCs in the aerosol of the three HeatSticks. The Applicant compared the quantity of each HPHC in the HeatSticks with data obtained from the Kentucky reference cigarette 3R4F. The comparison is performed per unit, which is a quantity in the aerosol of the HeatSticks compared with the quantity in mainstream cigarette smoke.

In the PMI-58 test, the aerosol is generated using modified Canadian intense smoking regimen. The method is modified because the HeatSticks have no ventilation holes to block. Modified Canadian intense smoking regimen uses the same parameters as the Canadian intense smoking regimen but with no vent blocking applied.

The next slide shows data from the PMI-58 study for Marlboro HeatSticks. This graph shows the residual level of HPHCs in the aerosol of Marlboro HeatSticks compared with HPHC levels in the smoke of the reference cigarette 3R4F. Similar residual levels are reported for Marlboro Smooth Menthol HeatSticks and for Marlboro Fresh Menthol HeatSticks.

The reductions observed are between 62 and 99.9%. Given that in the IQOS system the tobacco is heated at temperatures below 350 degrees Celsius, the HPHC levels formed by combustion and pyrolysis are expected to be lower than those in the smoke from combusted cigarette.

I want to point out some specific HPHCs that could be higher in the aerosol of the IQOS, given the tobacco blend and ingredients present in the HeatSticks.

Formaldehyde and acrolein are produced by glycerol and propylene glycol. Despite a higher level of glycerol and

propylene glycol in the HeatSticks and in combusted cigarettes, the level of acrolein is 95% lower in the aerosol of the HeatSticks than in the smoke of 3R4F, and the level of formaldehyde is 82% lower in the aerosol of HeatSticks than in the smoke of 3R4F.

The level of NNN and NNK could be higher in cigarettes containing reconstituted tobacco. The data shows that the level of NNN and NNK are 96 to 97% lower in the aerosol of the HeatSticks than in the smoke of the reference cigarette 3R4F.

Carbon monoxide and nitrogen oxide can be produced at high levels through the combustion of reconstituted tobacco. This data indicates that the level of carbon monoxide and nitrogen oxide is 97 to 99% lower in the aerosol of the HeatSticks than in the smoke of the reference cigarette 3R4F.

Ammonia and acrylamide are 63 to 65% lower in the aerosol of the HeatSticks compared to 3R4F. While there are lower levels of ammonia and acrylamide in the aerosol of the IQOS system, the reduction is not as significant as the reduction of several other HPHCs. Both ammonia and acrylamide could be formed at the temperature of operation of the IQOS system.

The Applicant also compared the quantity in aerosol of 18 HPHCs from the PMI-58 dataset with a medium quantity in

mainstream smoke from 31 Philip Morris USA cigarettes.

This slide shows the residual level of HPHCs in the aerosol of the Marlboro HeatSticks compared with the medium quantity in mainstream smoke from 31 Philip Morris USA cigarettes. Similar levels are observed for Marlboro Smooth Menthol HeatSticks and Marlboro Fresh Menthol HeatSticks.

The reductions observed are between 61 and 99.9%, which are similar as those observed when comparing the HeatSticks with the reference cigarette 3R4F.

As I mentioned earlier, PMI-58 data includes also nicotine level in the aerosol of the three HeatSticks obtained by modified Canadian intense smoking regimen.

Nicotine level is 1.29 mg per HeatStick in Marlboro HeatSticks, 1.19 mg per HeatStick in Marlboro Smooth Menthol HeatSticks, and 1.17 mg per HeatSticks in Marlboro Fresh Menthol HeatSticks.

For comparison, the nicotine level in the reference cigarette 3R4F is between 1.74 and 1.93 mg per cigarette, and the nicotine level in the mainstream smoke of 31 Philip Morris USA cigarettes is between 1.06 and 3.35 mg per cigarette.

The second analytical study that I will present is a non-targeted differential screening. The Applicant performed

non-targeted differential screening with a goal to identify and semi-quantify any constituent present in the aerosol of the HeatSticks at higher concentration compared to the smoke of the reference cigarette 3R4F.

The aerosol was generated by modified Canadian intense smoking regimen, and the analysis was performed by 2-dimensional gas chromatography combined with time-of-flight mass spectrometry and by liquid chromatography high-resolution accurate-mass spectrometry in full-scan modes. The semi-quantification is based on the relative peak areas.

The Applicant lists 53 compounds with higher quantities in aerosol of the Marlboro HeatSticks compared to smoke of 3R4F. In similar way, the Applicant lists 58 compounds in the Marlboro Smooth Menthol HeatSticks and 61 compounds in the Marlboro Fresh Menthol HeatSticks with higher quantities in the aerosol of the HeatSticks compared to smoke of 3R4F.

The compounds listed include menthol-related constituents, alkaloids, and flavors. Menthol-related constituents are expected to be higher since the comparison is performed against 3R4F, which is a non-mentholated cigarette.

The next slide shows selected compounds for which the levels in the aerosol of the HeatStick are higher than the

level in smoke of 3R4F.

Some compounds developed at the higher level in the aerosol are of concern. For example, propylene glycol is between 383 and 638% higher in the aerosol of the HeatSticks than in the smoke of the reference cigarette 3R4F. In similar way, acetol is 35 to 67% higher and glycidol is 108 to 224% higher in the HeatSticks than in 3R4F.

This slide shows the increase of all the compounds reported by the Applicant in the non-targeted differential screening of Marlboro HeatSticks. Similar increased levels are reported for Marlboro Smooth Menthol HeatSticks and Marlboro Fresh Menthol HeatSticks. The increases observed are between 13,650% and 20%.

As part of FDA assessment, analytical testing was performed to verify the Applicant's data. Testing of tar, nicotine, acrolein, formaldehyde, and benzopyrene in mainstream aerosol, and ammonia, NNN, NNK in the tobacco filler was performed at FDA's Southeast Tobacco Laboratory in Atlanta, Georgia.

The analytes tested were selected based on characteristic of the HeatSticks, such as tobacco type and ingredients, and also considered in constituents that are produced in mainstream

cigarette smoke.

While the methods were similar, they were not identical. For example, the Applicant used a 20-port linear smoking machine and Southeast Tobacco Laboratory used an e-cigarette smoking machine.

The levels of acrolein, formaldehyde, and benzopyrene measured by Southeast Tobacco Laboratory are higher compared to the values reported by the Applicant but significantly lower than the levels in the reference cigarette 3R4F. A reduction greater than 90% is observed for acrolein and benzopyrene and greater than 77% for formaldehyde in the HeatSticks compared to 3R4F.

This slide shows a comparison of the data obtained by FDA and the data submitted by the Applicant. I apologize because I understand this slide is a very busy slide, but I just want to point out to the data obtained for acrolein, formaldehyde, and benzopyrene.

The column headed "PMP SA data" include data from the Applicant, and the column headed "STL results" include the results obtained by Southeast Tobacco Laboratory. As I mentioned previously, the levels obtained by FDA are higher than the levels reported by the Applicant, but still, the data

show between 77 and 90% reduction for these three HPHCs.

In addition to performing the analytical testing, we also searched the published literature to identify additional studies that reported on the chemical analyses of heat-not-burn tobacco products.

These are three of the most relevant studies found in the literature. The main findings from these studies are summarized in this slide.

Auer et al. reported 18% reduction of acrolein and 26% reduction of formaldehyde in the aerosol of HeatSticks compared to the level in the smoke of one commercial cigarette. These reduction levels are significantly lower than the reductions reported by the Applicant. In addition, Auer reported high quantity of acenaphthene, and acenaphthene was not reported by the Applicant.

Our assessment of these publications indicates that we don't have enough information regarding the analytical methodology to be able to rely on these estimates in our evaluation.

Bekki et al. found 99% lower quantity of carbon monoxide and between 87 and 95% lower quantities of NNN and NNK in the aerosol of HeatSticks compared to mainstream smoke in the

reference cigarette 3R4F and also 1R5F. These findings are similar to the data reported by the Applicant.

The last paper that we have listed here from Savareear et al. from British American Tobacco focused on compounds other than HPHCs. They reported the presence of 205 compounds in the aerosol of HeatSticks. These compounds include flavor and fragrance agents, humectants, natural substances, and one plasticizer. The paper lists 82 compounds that were not previously reported in cigarette smoke. From those 82 compounds, 43 compounds were previously reported in tobacco leaves but not in cigarette smoke.

In summary, the Applicant states that the IQOS system heats but does not burn tobacco, resulting in significantly reduced concentrations of HPHCs.

The data submitted by the Applicant show that 54 HPHCs are between 54 and 99.9% lower in the IQOS system when compared per unit.

The independent testing performed found lower levels of selected HPHCs in the aerosol of the HeatStick compared to mainstream cigarette smoke.

However, the Applicant reported 53 compounds in the Marlboro HeatSticks, 58 compounds in the Marlboro Smooth

Menthol HeatSticks, and 61 compounds in the Marlboro Fresh Menthol HeatSticks with higher quantities in the aerosol of the HeatSticks. Compounds other than HPHCs, such as glycerol, acetol, and propylene glycol are higher in the aerosol of the HeatSticks compared to the mainstream cigarette smoke of the Kentucky reference cigarette 3R4F.

Thank you for your attention, and at this moment, I will take any clarifying question.

DR. HUANG: Okay, any clarifying questions?

Dr. Fagan.

(Off microphone response.)

DR. HUANG: Oh. Dr. Thrasher.

DR. THRASHER: So the data that you're presenting from the Applicant on the additional compounds, I'm not a chemist, so I'm struggling to understand how meaningful those additional compounds are and whether the assays that were done are really global enough to encompass any possible harmful or potentially harmful constituent. Can you help me understand that?

DR. ZUCK: Sure. The first test, the PMI-58, was a focus test. They looked for those specific compounds. So in the second, the non-targeted screening, although I have to say I didn't -- we are still evaluating, we don't have all the

information from the Applicant, we just have some information that came in on December.

But with information that we have, they are using methods that are more general, and they are able to identify a larger set of compounds without pinpointing to specific masses or specific UV absorption, so it's clearly a more general method and should be able to identify larger amount of compounds.

DR. THRASHER: So what's the likelihood that additional compounds of consequence are going to be left outside of the range of what would be captured with that method?

DR. ZUCK: Sure. I would say that -- so they used two different methods, a GC method and an LC method, and in, I believe, in each one of the methods, at least on the GC method, they used three or four, I don't remember, different analytical techniques to be able to include nonpolar compounds, polar compounds, polarity compounds. I cannot guarantee that there is nothing that is being left out, but it seems like a comprehensive approach, at least for what I can see up to now.

DR. HUANG: Could I follow up? Yeah, so the Savareear study reported 205 compounds that were not previously reported. So, again, are those potentially significant?

DR. ZUCK: I wasn't sure what the question was, but I

still am waiting and comparing the list submitted from the Applicant and from the paper. They are not all the same compounds. So I'm still on the process of comparing both, and not all the compounds reported on that publication are in the Applicant list and opposite.

DR. HUANG: Yes, Dr. Rees.

DR. REES: The Canadian intense method is used because it somewhat approximates real human smoking parameters of a conventional cigarette. Does it also apply to IQOS? Do people smoke the IQOS product in a way that they might smoke a conventional cigarette intensively? If so, is the yield of constituents in the smoke of the IQOS elastic? In other words, is more intensive puffing rewarded by greater delivery of nicotine to the consumer?

DR. APELBERG: Yeah, I was just going to add, I mean, we're going to have additional presentations including assessments of the actual use studies, the -- whatever topography information, consumption data are -- you know, were submitted in the application. So some of that may come -- I'm not sure if it will necessarily address your specific question.

DR. REES: Thank you, but I think -- I guess my question is has IQOS been tested using different machine yield

parameters? And does that influence the --

DR. ZUCK: So the Applicant submitted a test that -- it's the FDA 18+6, and another one we received later, the IQOS was tested under ISO and Canadian smoking condition, so we do have both set of data.

DR. REES: So how do they compare?

DR. ZUCK: Yeah, there is a larger amount in the Canadian intense than the ISO. I cannot tell you -- that's a good point. I cannot tell you if you compare the same relationship like in a combusted cigarette, but the quantities from the Canadian are higher than on the ISO.

DR. HUANG: There's no vent holes in the HeatSticks?

DR. ZUCK: No.

DR. REES: No indeed, which makes me wonder whether people smoke it intensively as they would do with a conventional product where the ventilation encourages intensive smoking and rewards intensive smoking --

DR. HUANG: That's a good question.

DR. ZUCK: Yeah, I would have to look into that. I cannot tell you if increase -- the ratio of increase between ISO and Canadian on the HeatSticks is on the same proportion that -- on the cigarettes.

DR. REES: And just quickly, the yields that you've reported here are adjusted for nicotine. Are they normalized for nicotine yields?

DR. ZUCK: These are not normalized for nicotine or per unit.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes, I just want to follow up on a question that I asked earlier, but I'll ask you a very similar question. In my read of the application, the referent group for the harmful and potentially harmful constituent studies is 3R4F. Is that your understanding as well?

DR. ZUCK: Yes, it's my understanding.

DR. FAGAN: Okay. Did you see anywhere in the application where there was a referent group for Menthol Fresh and Menthol Smooth that was equivalent?

DR. ZUCK: So --

DR. FAGAN: A cigarette referent.

DR. ZUCK: -- I do not -- I only focus on the chemistry data, and I did not see -- maybe I'm missing, but it's my understanding that for all the chemistry studies, the referent, the conducted cigarette 3R4F, non-mentholated, is used.

DR. FAGAN: Okay, thank you.

DR. HUANG: Any other clarifying questions? Oh.

(Off microphone comment.)

DR. HUANG: Dr. McKinney.

DR. McKINNEY: I'd like to make a statement, though. I think we have to be careful applying smoking standards, Canadian and ISO, to the way humans smoke cigarettes. Those tests are for comparative analysis and don't necessarily reflect the way that humans smoke cigarettes.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I was just curious why you didn't measure carbon monoxide in your list.

DR. ZUCK: I'm sorry, why we don't measure --

DR. GIOVINO: You didn't test carbon monoxide. I'm just so used to seeing --

DR. ZUCK: Oh, you mean --

DR. GIOVINO: -- and carbon monoxide.

DR. ZUCK: -- when we try to verify?

DR. GIOVINO: When you tried to verify, yes.

DR. ZUCK: You know, we have to select some -- we have certain amount of compounds that we could test, and clearly, that was the one that was initially on the list, but then we have to select some, so we just focused on some that we thought

were relevant.

DR. GIOVINO: Okay.

DR. HUANG: And we have Dr. Ossip on the line.

DR. OSSIP: Yeah, thank you.

A couple of things. One is just to follow up on the earlier question about are there other constituents that are in the IQOS but not in the reference cigarettes or combustible cigarettes. And the list that you present in Slide 16 from the study by British American Tobacco, do we have any other sources, maybe an independent source, that might have identified some additional constituents? That's the first question.

And then the second question is, and I suspect this may come up later as well, but from the standpoint of a chemist, if you could help us understand what the reduction in HPHCs, what that means relative to some absolute risk to -- is there some absolute thresholds of exposure? Is it a cumulative issue, if you have a lower exposure but cumulatively over time the risk remains the same, it just may take longer for it to become evident, or is there some -- for these particular items, is there some threshold where as long as it's below that threshold, irrespective of how you use it or how long you use

it, your risk is substantially reduced?

I ask this from your perspective just because ultimately, what we're being asked to do is to tie this back to health risks, so I'd be interested if you could help us interpret what we're seeing through that lens.

DR. APELBERG: This is Ben. Can I just jump in? I think I want to put that question on hold because we're going to -- our next talk is going to be around toxicology, and so that's part of that assessment.

But I also want to just put it in the context that this assessment of these additional chemicals that came in, in this non-targeted differential screening is still ongoing because, as Dr. Zuck mentioned, it came in relatively late in the process. But I do think that we might hear a little bit more from our next speaker in terms of the toxicological implications of, you know, both that data as well as the additional, the nonclinical data.

DR. HUANG: Okay, Dr. McKinney.

DR. McKINNEY: Yeah, I was wondering if you could provide a clarification on your analysis of constituents or should I say chemicals that are formed from heating or burning or pyrosynthesis versus, say, if an ingredient is added and it

simply transfers to the aerosol of the IQOS but it's different from an ingredient that was added to a cigarette. And I know we used the term "constituent." I just want some clarity on what we really mean.

DR. ZUCK: So I totally -- I use constituents just to include everything that could be there. We are still evaluating everything that the Applicant submitted that includes HPHCs and non-HPHCs compounds, and that's why I say constituents. Some could be just ingredients added or evaporated at the lower temperature. We are still evaluating the constituents submitted on the Savareear paper or in our publication. I'm trying to include everything on my evaluation of these points, and we are still looking at all the compounds, HPHCs or no.

DR. HUANG: Any other questions?

(No response.)

DR. HUANG: All right, thank you. We'll move on to the next presenter, Dr. Wright.

DR. WRIGHT: Good afternoon. I'm Dr. Mayo Wright. I'm a toxicology reviewer in the Division of Nonclinical Studies -- Nonclinical Science, I'm sorry, in the CTP Office of Science. I'm going to spend a few minutes talking about the potential

health risk of IQOS use with a focus on evidence of toxicity that was found in the application -- or nonclinical study, I'm sorry, submitted by the Applicant. Before I begin, I'd like to remind you of the disclaimer that was mentioned earlier.

So I'll begin my presentation by comparing chemicals found in HeatStick aerosols with those in referent cigarette smoke, including harmful and potentially harmful constituents or HPHCs.

I will also discuss in vitro studies submitted by the Applicant that determine cytotoxic and mutagenic potential of the products, including organotypic studies with human cell cultures that examine the pathophysiological effects of acute exposure to HeatStick aerosols and smoke from referent cigarettes.

Finally, I'll review evidence of potential toxicity from repeat exposure experiments with HeatStick aerosols and referent cigarettes using rodent models. This includes a switching and cessation study with some preliminary data from the study comparing the carcinogenic potential of HeatStick aerosols to referent cigarette smoke.

I should begin by noting, as Dr. Zuck just did, that levels of many of the HPHCs found in HeatStick aerosols are

reduced when compared to referent cigarette smoke. However, data submitted by the Applicant indicates that consuming 10 HeatSticks exposes users to levels of mercury, ammonia, acrylamide, butyraldehyde, acetamide, pyridine, formaldehyde, catechol, propylene oxide, and acetaldehyde that are comparable to smoking one to three referent cigarettes.

It should also be noted that a number of the HPHCs found in both HeatStick aerosols and in referent cigarette smoke are carcinogenic to humans or possibly carcinogenic to humans. These include acrylamide, acetamide, formaldehyde, catechol, propylene oxide, acetaldehyde, and others.

And just previously, the Applicant has recently submitted data identifying at least 12 possibly carcinogenic or genotoxic chemicals. They're found in higher levels in HeatStick aerosols than in referent cigarette smoke.

For instance, levels of glycidol in HeatStick aerosols are as much as 3.2 times the levels found in referent cigarette smoke. Glycidol is mutagenic in many nonclinical tests, and it's classified as a probable human carcinogen. For carcinogens that are mutagenic, like glycidol, cancer potency is assessed using linear extrapolation from the low-dose region of a dose-response curve. Using this model, any increased

exposure increases cancer risk.

The Applicant also submitted study reports for several in vitro assays that compared to cytotoxic and mutagenic potential of regular and menthol HeatSticks to referent cigarette smoke.

Among these assays was the Ames test. The Ames test detects mutagenicity in bacterial cells. In the Ames test, total particulate matter, or TPM, from referent cigarette smoke was mutagenic in three of the five bacterial strains tested, while HeatStick aerosol, HeatStick TPM, was not mutagenic under any of the conditions tested.

So while both referent cigarette smoke and HeatStick aerosols contain chemicals that are carcinogenic or possibly carcinogenic to humans, HeatStick aerosols did not produce a positive response in the Ames test under any of the conditions tested by the Applicant.

It should also be noted that the study reports did not contain information from an Ames with the gas vapor phase, or GVP, of the HeatStick aerosols. An Ames test with GVP would provide information about the mutagenic potential of HeatStick aerosols.

Also, the Applicant submitted study reports for the neutral red uptake test, or the NRU test. This test uses a

mammalian cell line to detect cytotoxicity. The NRU test results indicate HeatStick aerosols can be cytotoxic, but these effects are generally less severe and require higher levels of exposure than referent cigarette smoke. In the NRU test, TPM from HeatStick aerosols were about 90% less cytotoxic than TPM from referent cigarette smoke.

Also, the Applicant submitted study reports from the mouse lymphoma assay, or the MLA. The MLA is a test that detects mutagenicity in a mammalian cell line. HeatStick aerosols were positive for mutagenicity in the MLA, with toxicity occurring at higher concentrations than referent cigarette smoke. These graphs depict the known concentration of either referent cigarette smoke, here in the red bars, or HeatStick aerosols, in the gray -- in green bars -- produced a mutagenic effect. As you can see, there's a 15- to 30-fold difference in the potency of TPM from HeatStick aerosols and the referent cigarette smoke. There was a similar difference in mutagenic potency from the GVP of the products.

The MLA study did not contain information about clastogenicity or the capacity to cause damage to chromosomes directly. Also, while the MLA study, which is an in vitro test, indicates that HeatSticks are mutagenic, there

was no in vivo mutagenicity study information provided which could have further clarified the mutagenic potential of the products.

Also, the Applicant submitted study reports from five separate in vitro organotypic studies assessing the effects of acute exposure to regular HeatStick aerosols and referent cigarette smoke on human gingival, buccal, nasal, bronchial, and coronary artery epithelial cells. The results indicate that HeatStick aerosols generally produce fewer pathophysiological changes and adverse effects than referent cigarette smoke. For example, as illustrated in this figure provided by the Applicant, acute exposure to referent cigarette smoke produced significant cytotoxicity and histological changes in the bronchial epithelium that persisted for at least 72 hours after the last exposure, while HeatStick aerosols produced fewer effects and those effects were less severe.

And while HeatStick aerosols can have pro-inflammatory effects as well as adverse pathophysiological effects in buccal cell cultures and alter responses to oxidative stress in gingival cell cultures, those changes are less pronounced than effects of referent cigarette smoke and generally occur at higher concentrations.

Also, HeatStick aerosols increased cell adhesion and reduced monocyte migration in the coronary artery cell cultures at higher concentrations than referent cigarette smoke.

The Applicant also submitted some in vivo studies, including two separate 90-day nose-only rat inhalation studies with a 42-day post-exposure recovery period using both regular menthol HeatSticks as well as referent cigarettes.

In general, repeat exposure to aerosols produced fewer or less severe pathophysiological changes in the respiratory tract than exposure to referent cigarette smoke. However, some degeneration was observed in the larynx of rats exposed to either HeatStick aerosols or referent cigarette smoke. Also, concentration dependent increases in epithelial thickness in the floor of the larynx and the vocal cords occurred to a lesser extent in rats exposed to HeatStick aerosols and those exposed to referent cigarette smoke.

However, for squamous cell metaplasia, a potentially precancerous lesion, response produced in the larynx from HeatStick aerosols were similar to that of the referent cigarette smoke after the 90-day exposure period.

Data highlighted here in the red circle indicate that all animals exhibited some degree of squamous metaplasia after 90

days of exposure to either HeatStick aerosols or referent cigarette smoke. Data summarized in that panel also indicate that some rats that were exposed to high concentrations of either HeatStick aerosols or referent cigarette smoke continue to exhibit squamous metaplasia 42 days after the last exposure.

Also, the Applicant submitted a study report from an 8-month-long switching and cessation study with ApoE knockout mice. In this group, mice -- the group in this study included mice exposed to filtered air, referent cigarette smoke, or HeatStick aerosols 5 days each week for 8 months. The study also included a group that were exposed to the referent cigarette smoke for 2 months followed by 6 months of filtered air. This condition mimics or models smoking cessation. The study also included a group that was exposed to referent cigarette smoke for 2 months followed by 6 months of HeatStick aerosols. This conditions models, is intended to model switching from cigarettes to HeatSticks.

I'll just take a moment to orient you to these graphs. The data in the blue bars are from rats exposed to filtered air, and it's the sham condition. The data in the gray bars are rats exposed to referent cigarette smoke. The data in the orange bars are from rats exposed to HeatStick aerosols. The

yellow bars are from the cessation condition. And the green bars are from the switching condition.

So the histopathological findings from this study indicate that 8 months of referent cigarette smoke increases mean vocal cord length, destructive index, and emphysema score, and decreased the number of bronchial attachments compared to other groups.

These data are all indices of respiratory toxicity. However, mice that were only exposed to HeatStick aerosols, mice that switched from referent cigarette smoke to HeatStick aerosols, mice that underwent cessation or were only exposed to sham conditions all had similar histopathological characteristics.

These data suggest that switching to HeatStick aerosols after a relatively brief period of exposure to referent cigarette smoke produces histopathological changes that are similar to cessation. It is unclear, however, if longer periods of cigarette smoke exposure produced similar results.

Also in the study, biomarkers of exposure to carbon monoxide, acrolein, shown here on the left; NNK, shown here on the right; benzene and acrylonitrile, as well as some biomarkers of oxidative stress and inflammation were elevated

in the ApoE knockout mice exposed to referent cigarette smoke, but not in mice exposed to HeatStick aerosols or filtered air.

And, finally, the Applicant submitted preliminary data from a partially completed study with A/J mice to determine the carcinogenic potential of HeatStick aerosols and referent cigarette smoke.

After 10 months, neoplastic lesions, like some adenomas, were found in the lungs of female mice exposed to either referent cigarette smoke or HeatStick aerosols.

Also, the incidence of neoplastic lesions in general appeared to be higher in some groups exposed to HeatStick aerosols or referent cigarette smoke than in the sham control group.

It should also be noted that the study with male mice was terminated after 15 months due to the high number of deaths in the mice exposed to the highest concentration of HeatStick aerosols.

So, in summary, while HeatStick aerosols demonstrate potential toxicity under conditions tested by the Applicant, the effects were generally fewer and less severe than what was observed with referent cigarette smoke.

When HeatStick aerosols did induce toxicity in the

in vitro or in vivo studies, toxicity occurred at higher concentrations when compared to referent cigarette smoke.

Also, HeatStick aerosols did not produce additional adverse effects beyond those observed in the test groups that were exposed to referent cigarette smoke.

In recent studies that were submitted, however, it is unclear if the effects that were observed in these treatment groups can translate to potential risk reduction for non-cancer-related effects when chronically used by humans.

Thank you for your attention, and I'll take any questions you may have now.

DR. HUANG: And maybe we'll start by following up with Dr. Ossip's question in the last group.

Dr. Ossip, do you want to repeat your question or --

DR. OSSIP: Yeah, thanks. The question was if you had to put this into context for us about -- so use in different levels of some of these constituents that are different between the IQOS and the referent cigarettes or the comparator cigarettes, but -- if you could talk about the implications of this.

So is it that this period of study is appropriate for demonstrating the actual potential impact on health once you

expect a different time course for, say, the referent cigarette compared to the IQOS cigarette?

If you have something to which users are exposed at a lower level, for example, is there a threshold that's sufficiently low that we can say with some confidence that this truly is a long-term reduced risk product, or is the risk at the level where, with repeated exposure over time, there just may be a different time course for development of the particular adverse health outcomes?

So I realize there are a number of questions in there, but what I'm asking you is to interpret this for us in a way that we can assess was the methodology appropriate to identify anything that might become evident in the IQOS over time, perhaps it's a different time frame, or conversely, to be able to interpret with greater confidence that a reduction, in fact, means a reduction in risk.

DR. WRIGHT: So I guess there are a couple of different answers to that question or those questions. The first is that -- and some of them are only by analogy. We know that smoking only a few cigarettes a day does produce long-term health consequences, and we know that smoking 10 HeatSticks a day gives you similar levels of some HPHCs to smoking one to

three referent cigarettes. So those are indirect data suggesting that there could be long-term consequences.

Unfortunately, however, this requires time to study, and animal models aren't always exact. Of course, they don't predict precisely. The Applicant gave us a lot of information. A lot of it was from acute studies; a lot of it was from studies with naive animals. We have a switching condition where the exposure was for about 10% of the rat's life -- the mouse's life, sorry. And then we followed up. So if we had longer exposure periods, would that change the outcome? We simply don't know. It's an empirical answer, but we don't have the answer right now. I'm sorry I couldn't give you a more precise answer, but to this point that's the best I can do.

DR. OSSIP: Thank you.

DR. WRIGHT: You're welcome.

DR. HUANG: All right. Dr. McKinney.

DR. McKINNEY: Yeah, let me follow up on that question. Wouldn't a really true risk assessment factor in all of the data? And I think we've only heard a component. We've heard the chemistry, we've heard kind of the tox, and then there's clinical, and there's some more data. Would you agree with that?

DR. WRIGHT: Yes.

DR. McKINNEY: Okay.

DR. HUANG: Dr. Thrasher.

DR. THRASHER: In your summary, you raise some concerns about the clarity of the effects with regard to non-cancer-related outcomes. Does that include cardiovascular effects which are, again, a substantial piece of the puzzle for tobacco-attributable risk?

DR. WRIGHT: It could. We see less inflammation which, of course, is a big player in that, and we see a reduced monocyte migration in these models, but it doesn't say it doesn't exist. So I would say that there appears to be some effect there, and it is less than we see with the referent cigarette exposure, but I'm not able to give you an absolute comparison.

DR. THRASHER: So, in terms of the weight of evidence, it's more in favor of cancer-related outcomes as opposed to cardiovascular-related outcomes; is that right?

DR. WRIGHT: Because our course of study is not yet completed, we have only preliminary data, and because the duration of exposure in other studies was fairly limited, it's hard to make that call. So I don't know that it is more weighted to other toxicity. I will tell you that human

equivalent exposures, as we saw for glycidol, are based on tumor formation and other types of -- sorry, toxicity. So we still have to think about that for the elevated constituents in the recent --

DR. THRASHER: On a related point, the total particulate matter that you're looking at, which does pop out a little bit as being higher, I guess, for the HeatSticks, is that right?

DR. WRIGHT: It's just different. It has a different composition; it's a much wetter kind of aerosol than you get from the cigarette. It has fewer carbon components. It has a different chemical composition. But is there more of it? I don't think there's actually -- on a per stick basis, I'm not sure if there's more of it or not, to be honest with you.

DR. THRASHER: Okay. And sorry, just one more follow-up point, then I'll be done. Are there other kind of ultra-fine particulates or other kinds of particulates that are not captured by the total particulate matter measurement?

DR. WRIGHT: The evidence from the Applicant is that there are very few ultra-fine particles in this aerosol.

DR. THRASHER: Okay, thank you.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: I'm sure we'll come back to this, but from

what you've evaluated, are there any effects that are worse or any evidence that these agents are worse than are cigarettes?

DR. WRIGHT: No.

DR. HUANG: And my apologies. Actually, we had one of our participants join late. Dr. Hecht, maybe you might want to introduce yourself first and then --

DR. HECHT: Steve Hecht, University of Minnesota.

In the data you showed from the A/J mouse study, you didn't present tumors per mouse, lung tumors per mouse, which is the usual way of scoring those studies. What was the result?

DR. WRIGHT: So the A/J mouse study is a preliminary report; there were no stats run on this. There's not a lot of detailed information in the study regarding those kinds of issues. I can pull this data out. I'd be glad to have slides for you later -- tomorrow perhaps -- to tell you what is there, but I couldn't tell you off the top of my head what the answer is.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: In your review of chemicals like glycidol, can you help me understand the relationship of your review versus what we were told earlier about the threshold of

toxicological concern?

DR. WRIGHT: So as I alluded to a moment ago, the human equivalent exposure or concentration that was used to calculate the 1:39 ratio for glycidol, that is, 1/39th of the threshold dose, those are based upon tumor studies; they aren't on complete toxicity. So we are evaluating those data as a recent submission. We are evaluating those data -- I think that's the extent of what I can tell you right now, though.

DR. McKINNEY: And I guess the primary -- those data show a threshold?

DR. WRIGHT: They do.

DR. McKINNEY: Okay. And -- okay, thank you.

DR. WRIGHT: Sure.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes, thank you.

I just want to clarify this definition of switching for the animal studies.

DR. WRIGHT: Yes.

DR. FAGAN: Here I see it's 2 months of cigarette smoking followed by 6 months of exclusive HeatStick --

DR. WRIGHT: Correct.

DR. FAGAN: -- is that correct?

DR. WRIGHT: That's correct.

DR. FAGAN: Okay. I'm just trying to make sure we have a clear understanding of how switching is defined in the animal studies and then how we are defining or the Applicant is defining switching in some of the human studies.

DR. WRIGHT: Right.

DR. FAGAN: So I just wanted to clarify that that's what it is.

DR. WRIGHT: That's right. There is no dual use condition in that study.

DR. FAGAN: And no partial or anything. It's just exclusive, okay.

DR. WRIGHT: That's correct.

DR. FAGAN: Thank you.

DR. WRIGHT: Sure.

DR. HUANG: Anything else?

(No response.)

DR. HUANG: All right, we'll move on to the next presentation. Dr. Konkel.

DR. KONKEL: Good afternoon. My name is Dr. Karen Konkel, and I'm a medical officer in the Center for Tobacco Products. I will be discussing some of the evidence related to the health

risks of IQOS use.

This is the standard disclaimer.

I've included a list of acronyms that will be used in this presentation. I will not go through this list, but they are available for your reference.

To get started, I'd like to briefly describe what I'll be covering. I will include a review of the hypothesis, a summary of the human studies submitted, a preliminary assessment of the reduced exposure, or REX, studies. I will begin with a graphic that summarizes the Applicant's hypothesis.

The Applicant's hypothesis is that through heating instead of burning tobacco, the product will produce less harmful or potentially harmful constituents, which I will refer to as HPHCs. Users will therefore have less exposure, leading to favorable changes in biomarkers of potential harm. Such improvements may represent potential for reductions in cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer.

To support this hypothesis, the application included pharmacokinetic and pharmacodynamic studies, reduced exposure clinical studies, an actual use study, published clinical reports, perception and intention studies, and epidemiologic

studies. I will focus the rest of this presentation on the reduced exposure studies with attention to the biomarkers of exposure and the biomarkers of potential harm.

The four reduced exposure studies were designed to investigate systemic exposures to 16 compounds, 15 of which are on FDA's HPHC list. The sixteenth is pyrene, a polycyclic aromatic hydrocarbon that isn't on the list, and I will comment on this later.

The Applicant used a randomized, controlled, open-label, parallel, three-arm design in which the applicants -- excuse me, the participants were to use the assigned product as they wished. Subjects all smoked at least 10 cigarettes per day for the past month and had no intent to quit.

The three arms were as follows: Half of the participants in each study were assigned to IQOS, and the remaining half were evenly assigned to either their own brand cigarette or smoking abstinence.

Now let's take a look at the table. Studies 3 and 4 were completed in Poland and Japan, respectively. They used regular flavored tobacco products and were 5 days in duration. The participants remained in confinement for those 5 days. Studies 7 and 8 were conducted in Japan and the United States,

respectively. They used menthol products. Participants were monitored for 5 days of confinement followed by 85 days of ambulatory observation. During the second portion of the study, the subjects were requested to use their assigned products exclusively.

Several outcomes were measured. These included biomarkers of exposure, biomarkers of potential harm, nicotine exposure, tobacco product consumption, topography, and subjective effects.

Now that I've presented a brief overview of the REX studies, I will talk more about biomarkers of exposure followed by biomarkers of potential harm. In an upcoming presentation from my pharmacology colleagues, we'll focus on evaluation of endpoints related to abuse liability and nicotine exposure.

The Applicant chose 16 biomarkers of exposure to evaluate systemic exposure to HPHCs or pyrene. Their selection criteria were based on whether the biomarker of exposure represented both chemical and organ toxicity classes, reflected specific toxic exposure, or was a reliable surrogate of exposure, represented a broad range of formation temperatures, were highly specific to cigarette smoking, could be reliably detected using validated reproducible and precise methods, and

had a half-life suitable for the scheduled measurements.

Fifteen of these biomarkers represent exposure to compounds that are on the FDA's HPHC list of '93. Pyrene, a polycyclic aromatic hydrocarbon, or a PAH, is not on the FDA's HPHC list. However, a major metabolite of pyrene is 1-hydroxypyrene, which is a surrogate biomarker of exposure for all PAHs.

This slide, which is taken from the application, lists the selected biomarkers of exposure along with the HPHC or compound that it represents. I won't discuss these individually, but I will go over the related findings shortly.

Now I'd like to move on to the biomarkers of potential harm. These were referred to in the application as clinical risk endpoints, and they were defined as "a measure of biological process, physiological system, and/or mechanism of action that is associated with or known to contribute to smoking-related disease."

Several of these were measured as either secondary or exploratory endpoints to evaluate whether reportedly reduced HPHC exposure with IQOS could lead to an associated biologic change that might indicate the change in long-term disease risk, particularly for cardiovascular disease, COPD, and lung

cancer.

The Applicant's selection criteria required there to be evidence of an association with smoking, a relationship to at least one smoking-related health outcome, reversibility with smoking cessation, biologic plausibility, and dose response or temporality.

Based on these criteria, several endpoints were measured; however, six were singled out by the application for consideration. This was based upon the mechanistic association with three tobacco-related diseases of interest: cardiovascular disease or CVD; chronic obstructive disease or COPD; and/or lung cancer. Those pathophysiologic mechanisms are endothelial dysfunction, oxidative stress, lipid metabolism, inflammation, lung function, and platelet activation.

So now let's look in more detail at these markers. This table contains information from clinical monographs provided in Section 6 of the application.

The first one I'll discuss is soluble intercellular adhesion molecule, also known as sICAM or sICAM-1. This is considered a measure of endothelial dysfunction. It enables leukocytes to respond to inflammation by binding to endothelial cells and migrating into the sub-endothelial space. It is

found in atherosclerotic plaques and has been associated with cardiovascular disease and COPD.

The second is 8-epi-PGF2alpha, a measure of oxidative stress. It is a non-enzymatic, free radical-catalyzed peroxidation product of arachidonic acid. It has been associated with cardiovascular disease and COPD.

HDL-C stands for high-density lipoprotein cholesterol. It is one measure of lipid metabolism. It is believed to have anti-inflammatory, anti-oxidative, anti-apoptotic, and vasodilatory properties. It may also inhibit platelet aggregation or stickiness. In general, increases in HDL-C are considered physiologically favorable. It is inversely associated with cardiovascular disease. A small number of studies suggest a direct association between HDL-C and COPD. There is also weak and limited evidence of a direct link between HDL-C and lung cancer.

The white blood cell count is a measure of inflammation. It increases with smoking. There appears to be an association independent of smoking between white blood cell count, coronary atherosclerosis, atrial fibrillation, and peripheral artery disease. And an elevated white blood cell count is also associated with COPD.

The next measure is forced expiratory volume in one second, or FEV1. This is a measure of lung function. It reflects the severity of COPD. It decreases with age in both smokers and nonsmokers. The rate of decline in FEV1 over time, designated beta, occurs faster in smokers.

Finally, 11-dehydrothromboxane-B2 is considered a marker of platelet activation. It is a degradation product of the potent platelet aggravator thromboxane A2.

We've discussed the Applicant's hypothesis, and I've just presented a summary of clinical evidence submitted by the Applicant. Next, I will provide preliminary assessment of the reduced exposure studies.

In Reduced Exposure Studies 3 and 4, one arm of participants was switched from regular flavor combusted cigarettes to regular flavor IQOS. As a reminder, both studies had the same study design and involve 5 days of confinement, but Study 3 was done in Poland in the European Union, and Study 4 was completed in Poland. Excuse me, it was completed in Japan.

Comparing baseline to Day 5, there was substantial reduction in selected biomarkers of exposure. This reduction ranged from 47 to 96% and was similar to the smoking abstinence

arm.

This slide demonstrates the changes graphically. So let me orient you to these graphs. The top panel is from Study 3 from Poland in the European Union. The bottom panel is from Study 4 in Japan. The 16 biomarkers of exposure are listed on the x-axis, and the y-axis lists the percent change in geometric mean levels between baseline and Day 5. The darker bars represent smoking abstinence, and the lighter bars represent IQOS.

As you can see, most of the markers decrease from baseline and are similar in IQOS and in the smoking abstinence arms.

A couple of other points about the graph. S-BMA is an outliner -- outlier, excuse me. The findings for this biomarker of exposure to toluene are inconsistent in the reduced exposure studies, and that may relate to its lack of specificity. It can be elevated when people are exposed to benzyl alcohol, which is found in many common personal products like shampoo.

Then the little hashtag over NNN is another outlier, and that's in the THS arm, and the percent change from baseline values for total NNN are reported as median both for the tobacco heating system and the smoking abstinence arms.

The 90-day study showed statistically significant percentage reductions between baseline and Day 90 in 15 of the biomarkers of exposure, ranging from 34 to 92% in Japan and 15 to 82% in the United States. Note that these ranges exclude S-BMA and nicotine equivalents.

Again, here are the data graphically. The top panel shows the data from the 90-day study in Japan, and the bottom panel shows the data from the 90-day U.S. study. While there is still a decrease in the biomarkers of exposure with the use of IQOS, it is less pronounced in the 5-day studies.

Some additional things to point out: S-BMA continues to appear as an outlier. In the Study 7, the footnote there for ortho-toluidine, because of outliers in the tobacco heating system and the smoking abstinence arms, the percent change from baseline values for o-toluidine were reported as median for both arms. And then the footnote for Study 8, because of the limited number of subjects in the smoking abstinence arm and outliers, percent change from median -- excuse me, percent change from baseline values for total NNAL and HEMA are reported as median for both the tobacco heating system and smoking abstinence arms.

Switching gears, I'll now discuss data for the six

selected biomarkers of potential harm as measured in Reduced Exposure Studies 7 and 8. The results are represented as either the difference in the marker between IQOS and combusted cigarettes or as the percent reduction in the IQOS relative to combusted cigarettes. The ones that are statistically significant are in bold.

As you can see in the Japan study, there were reductions in white blood cells, soluble intercellular adhesion molecule, and 8-epi-PGF2alpha. There was an increase in HDL cholesterol. There was a reduction in soluble intercellular adhesion molecule in the United States study.

So I would like to provide the following preliminary assessment. The limitations of the reduced exposure studies include that a short duration could fail to detect changes in biomarkers of potential harm that take longer to develop. The results may not generalize to the U.S. population of smokers because the subjects were healthy and on no medications. There was only one United States study; this could lead to potential confounding by genetic and cultural differences. The United States study only included menthol smokers. The exposure reductions were reported among those who adhered to the study protocol, and specific data for exposures in incomplete

switchers or dual users was not provided.

Limitations of the measured biomarkers of potential harm include the analysis only considered secondary or exploratory endpoints which are not hypothesis driven, the biomarkers were neither tobacco specific nor disease specific, and the clinical significance of the differences observed is uncertain.

In conclusion, it is not clear whether or how much the chosen biomarkers of exposure and potential harm in the reduced exposure studies are predictive of long-term tobacco-related disease risk.

Thank you for your attention, and I can take any clarifying questions.

DR. HUANG: Any clarifying -- yeah, Dr. O'Connor.

DR. O'CONNOR: So I notice, both in the graphs that you presented as well as the ones that were presented earlier by the Applicant, that particularly in the U.S. study compared to the Japan study, that there -- the error bars are much larger in the U.S. study than they are in the Japan study for all of the biomarkers reported.

So, one, what were the dropout rates like, particularly in that 90-day study? And, two, are there other potential factors that could weigh into the greater observed variability in the

U.S. sample compared to the Japan sample?

DR. KONKEL: So one moment. Let me see if I can find the right slide number. So in the biomarkers of exposure, the error bars are much larger in the Japan versus the U.S. study. There is more variability there. I would like, if I may, defer the study -- defer this question to one of my colleagues.

DR. APELBERG: Yeah, can I jump in? I think part of the reason for the larger error bars is that, as I think was mentioned earlier by the Applicant, that this main analysis is the per-protocol analysis, and I believe there was a greater degree of compliance with the protocol in the Japanese study compared to the U.S. study. So some of it, you know, as I think you're alluding to, relates to the number of observations, you know, that were still sort of left in that analysis. But I believe the Applicant did run a range of different analyses including the full analysis set, everybody that was randomized, those who were fully compliant, and those who met the protocol, per-protocol criteria.

DR. HUANG: Yeah, Dr. Fagan.

DR. FAGAN: I have two questions. The first question is, what was your interpretation of the definition of switching for the REX studies? I'm trying to get an understanding of this

definition. As we go across studies, I'm trying to get an understanding of a consistency at which switching is defined, and so I'm just trying to get an understanding. We just went from the animal studies. Now we're --

DR. KONKEL: Um-hum.

DR. FAGAN: -- beginning to talk about human studies, and what was the interpretation of switching defined here in these studies? That's question number 1.

DR. APELBERG: I can jump in on this, too, because it's kind of related to the previous answer, and it was also related to what the Applicant said earlier. So in the 5-day confinement study --

DR. FAGAN: Um-hum.

DR. APELBERG: -- I mean, that's complete switching, as we think of complete, 100 percent, because the individuals are in confinement and are monitored. In the ambulatory part of the two studies, there are essentially different analyses that were done, there's this per-protocol analysis which has a certain criteria.

I think you guys, they had mentioned it earlier, I don't recall exactly what that threshold was, but it wasn't -- it allowed for some deviation from the protocol. But I believe

the information is there in the application to be able to analyze the results in different ways.

DR. FAGAN: Okay. And then my -- thank you, Ben. My second question has to do with the inclusion criteria -- well, not the inclusion criteria, but the type of participants in the U.S. study. So you have 160 people, and as you were reading through the data, was there any information related to the gender, age, and racial/ethnic composition for those 160 people?

DR. KONKEL: I believe there were. I know that they were similar with regard to age and gender, and they all had been smokers for at least 3 years. With regard to ethnicity, I don't know how much stratification there was, and one of my colleagues, Dr. Mishina, may be able to help me with the answer to this question.

DR. MISHINA: My name is Elena Mishina, and I'm in clinical pharmacology here at CTP. I have reviewed the studies and design, and I did some data analysis on this as well.

There was about 40% of black people in the U.S. Study 08, and I can comment, additional comment, on the hybrid utility and differences in different exposure to biomarkers of exposure because there was such a different variability in genetic

factors and there was more homogenous population in 07 study in Japan.

DR. FAGAN: Do you know what the -- for the U.S. sample, what percent of women were in the study, and do you know, was -- with regard to age group, did we have some representation of young adults? Do you know what percentage of 18- to 25-year-olds were in that study?

DR. MISHINA: I cannot tell you from the top of my head right this, but regarding the gender, there was about the same amount of male and female. I think it was a little bit more female than male.

DR. FAGAN: Okay, thank you.

DR. HUANG: We do have a question on the phone from Dr. Ossip.

DR. OSSIP: Yes, thank you. You mentioned that under your limitation section, that -- you mentioned a short duration and they failed to detect changes, and you also said that biomarkers were neither tobacco specific nor disease specific. So my question is are there particular biomarkers or measures that typically would be reported or would be expected to be reported that are not available in what we're looking at?

DR. KONKEL: I think that there were several other

biomarkers that were measured within the study that were not reported. This was a very specific set of biomarkers that were reported that I provided to you. There are other, many other biomarkers that were measured; all were kind of secondary or exploratory. So I don't think that I've covered everything that there possibly could be. I'm not sure if that answers your question.

DR. OSSIP: My question was, so you identified, I think, important limitations --

DR. KONKEL: Um-hum.

DR. OSSIP: -- that the clinical significance of the change in the biomarkers -- it's not clear how to evaluate what implications the results might have for disease risk.

DR. KONKEL: Um-hum.

DR. OSSIP: So my question was, would there typically be things that would be reported that either were done and not -- perhaps were done and not reported by the Applicant or that -- or perhaps should have been and were not or might typically be reported for comparable evaluations?

DR. KONKEL: Dr. Faulcon.

DR. FAULCON: Yes, hi. This is Lisa Faulcon. I am a team lead and medical officer in the Center for Tobacco Products,

Office of Science, in the Division of Individual Health Sciences.

And I just wanted to clarify that FDA hasn't established a set of biomarkers that we require applicants to test or to provide specific information on regarding health effects, health risks, or specific tobacco-related diseases.

So, you know, in that regard, we've evaluated what the Applicant put -- the information that they presented, and we sort of summarized that here for you, but we haven't required applicants to provide specific data on this specific set of biomarkers.

DR. OSSIP: Okay, thank you.

DR. FAULCON: You're welcome.

DR. HUANG: Dr. Rees.

DR. REES: Is there any analyses that look at variations in biomarkers of exposure according to consumption measures, specifically level of dependence and consumption through the 90- or 85-day period?

DR. KONKEL: So variability in the biomarkers of exposure based upon the level of use, is that what you mean?

DR. REES: Level of dependence --

DR. KONKEL: The level of --

DR. REES: -- of participants as they enter the study. We heard some details or some questions about the impact or the influence of race and ethnicity --

DR. KONKEL: Um-hum.

DR. REES: -- and gender and so on --

DR. KONKEL: Um-hum.

DR. REES: -- and I'm wondering whether level of dependence and consumption through the trial was reflected in levels of exposure biomarkers.

DR. KONKEL: I don't recall seeing anything in that regard. I can consult with my pharmacology colleagues that looked at dependence and abuse liability and see if they have any further information than I do. I don't know off the top of my head. I'm seeing some shaking heads back there saying no, we did not see any of that data.

DR. HUANG: Dr. Thrasher.

DR. THRASHER: So concerning the biomarkers of potential harm, it's striking to me that there's -- in the U.S. sample, at least, there's one out of the five that are shown here, or six that are shown here, that stands out as statistically significant.

Is this an issue of statistical power? Is it an issue of

the amount of time that people were followed up? So if you were following the statistics here, there wouldn't be very many biomarkers of potential harm that would be popping up.

DR. KONKEL: Right. Yeah, so I think that it could partly be statistical power and the duration of the study, although -- Caryn, can you back to Slide -- one moment, please. Can you go back to Slide 21, please?

So the white blood cell count, for instance, has been -- purportedly takes between 6 weeks and 6 to 12 months to decrease in a smoker who has ceased smoking, according to the information that was provided in the application. So whether or not that would be borne out to change over the course of a longer period of time than 90 days, I think I don't know that for certain. How much of this is statistical power, I don't know, I'm not a statistician, but that may have some influence on it.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: So I wanted to go back to the question, a variation on the question that Dr. Ossip coined. So as best I understand, there are 17 different cancers that have now been -- there's consensus -- are caused by tobacco exposure, and yet lung cancer was the only endpoint related to cancer.

Do you find that -- do we know about biomarkers of those other cancers, and is it an important limitation of what we've been presented with that there aren't data necessarily speaking to those?

DR. KONKEL: I think that's a good point. The Applicant provided lung cancer as the disease that they wanted to look at, but certainly, there are plenty of other cancers and other diseases that were not contained within this analysis.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Just to follow up a bit, I've been wondering about these biomarkers of potential harm as well, and the tables that you're presenting and the Applicant presented do show six. One of the public commentators, Dr. Glantz, presented some data with 24 biomarkers from the U.S. study.

DR. KONKEL: Um-hum.

DR. GIOVINO: Only the soluble ICAM was statistically significant --

DR. KONKEL: Right.

DR. GIOVINO: -- from the referent cigarette.

DR. KONKEL: Um-hum.

DR. GIOVINO: And, you know, I haven't been able to identify in the application all 23 of them, but have you had a

chance to compare what that public comment basically showed with what's in the application? I mean, have you had a chance to verify what that commentator said?

DR. KONKEL: I have preliminarily started to review that. I haven't gone through it all, but I am aware that the soluble intercellular adhesion molecules, the one that stood out as being statistically significant --

DR. GIOVINO: So if he's right, it's 1 out of 24, which you'd expect by chance --

DR. KONKEL: Um-hum.

DR. GIOVINO: -- which is important to know.

DR. HUANG: Any other clarifying questions?

(No response.)

DR. HUANG: All right, thank you. We'll move on to the next presenter.

DR. KONKEL: Thank you.

DR. HUANG: Drs. Rass and Mishina.

DR. APELBERG: Before Dr. Rass gets going, can I just make a clarifying statement about the biomarker discussion, I think, just to reiterate a few things, one which was previously mentioned that, you know, FDA doesn't have some set of biomarkers that are required or even necessarily strongly

recommended.

And we have had a number of workshops to talk about biomarkers, and biomarkers of potential harm was one of those, and I think everyone in that workshop sort of recognizes the challenge of, you know, sort of the lack of specificity of biomarkers of potential harm, the time frame needed to assess changes and to interpret what those mean for disease risk. And so I did just want to sort of make that point clear, as well as make the point that, Dr. Giovino, you mentioned the public comment. So yes, for sure we're evaluating all the substantive public comments that come in as well as assessing all of the material that's part of the application.

But what was brought here was to highlight sort of the key points, and with the biomarkers of potential harm, really highlighting the ones that were either primary or secondary endpoints, you know, sort of the focus of the study. But part of our assessment is evaluating all of the -- you know, all of the endpoints that are included in the studies.

DR. RASS: Good afternoon. My name is Dr. Olga Rass, and I'm a pharmacologist at CTP. Today I will be speaking about the evidence related to the impact of IQOS on tobacco users.

Here is the disclaimer slide.

I'm going to start by providing an overview of the clinical studies, focusing on study design aspects relevant to behavioral and clinical pharmacology.

Next, I will present results from these studies on the topic areas of nicotine exposure, product use and consumption behavior, and abuse liability.

Finally, I will summarize the overall conclusions.

This is a list of acronyms for your reference.

The Applicant provided data from four studies focusing on pharmacokinetics and pharmacodynamics. I will refer to these as the PK/PD studies. The studies refer to the IQOS system as the tobacco heating system or THS2.2. This is reflected in the slide.

The PK/PD studies evaluated the single use of a product after 24 hours of abstinence. Participants were randomized to one of two groups. Group 1 used IQOS on one visit and smoked their own brand cigarette on another visit. Group 2 used IQOS on one visit and used nicotine replacement in the form of gum or nasal spray on another visit.

Order of product use was counterbalanced. The studies were designed for within-subject analysis. Two studies used regular-flavored tobacco products, and two used menthol-

flavored products. The pharmacokinetic objectives were to compare the rate and extent of nicotine uptake measured by Cmax and AUC.

The pharmacodynamic measures compared craving using the Questionnaire of Smoking Urges, or QSU-Brief, and reinforcing effect using the modified Cigarette Evaluation Questionnaire, or mCEQ.

The Applicant provided data from four studies focusing on reduced exposure. I will refer to these as the REX studies. The study objectives were to measure changes in biomarkers of HPHCs.

Prior to randomization, participants tried the IQOS HeatSticks and agreed to being assigned to the IQOS/own-brand cigarette or smoking abstinence study arms. All four studies included 5 days of exclusive product use in confinement. Two of the studies had an extended ambulatory period for 85 days where participants were asked to use their assigned product exclusively in a naturalistic setting.

Outcome measures were compared between study arms. Relevant measures were systemic exposure to nicotine, tobacco product consumption, topography, and subjective effect questionnaires which included the Questionnaire of Smoking

Urges, the Minnesota Nicotine Withdrawal Scale, the Fagerstrom Test for Nicotine Dependence, and the modified Cigarette Evaluation Questionnaire.

The Applicant provided data from one actual use study where participants were asked to use the IQOS in a naturalistic setting. This prospective observational study design is similar to the ambulatory period of the REX studies, but no instructions were given to the participants regarding exclusive use.

Data were collected for a 1-week baseline of own-brand cigarette use followed by 6 weeks of access to free IQOS. Participants could request regular, menthol, or both flavors. Relevant outcome measures included tobacco product consumption, a hypothetical purchase question, and IQOS misuse. Data on these patterns will be discussed in a separate presentation.

The results of the studies were interpreted in the context of several study design limitations. In all three study designs, participants were a convenience sample of smokers, so the data are not nationally representative of U.S. adult smokers. Participants also had no intent to quit in the next 6 months or 1 month, so data may not generalize to smokers with different quit intent goals. In the PK/PD and REX studies,

participants were moderate to heavy smokers. The data may not be generalizable to light and non-daily smokers.

In the REX studies, the two 90-day studies were conducted with products containing menthol in a sample of menthol smokers; therefore, the results do not generalize to non-menthol products.

In the REX and actual use studies, the IQOS system and HeatSticks, but not own-brand cigarettes, were provided free of charge. This may result in increased use rates of IQOS.

Finally, all of the studies using the menthol HeatSticks used a high menthol variety; therefore, the data may not generalize to the low menthol HeatStick.

Moving on to results.

Nicotine systemic exposure was measured in the PK/PD and REX studies. In the PK/PD studies, nicotine exposure was lower for IQOS relative to cigarette smoking in two studies. In the other two studies, nicotine exposure was similar for IQOS and cigarette smoking. These differences may be explained by different nicotine yields of cigarette comparators in different countries, greater IQOS awareness or experience in the Japanese population where IQOS is available for purchase, and genetic differences in nicotine metabolism across studies and

participants.

In the 90-day REX studies, systemic nicotine exposure was similar between IQOS and cigarette smoking arms in the ambulatory period. It is important to note that dual use was evident in these studies. Because there was no stratification of complete versus incomplete switchers, it is not possible to tell whether nicotine exposure is due to IQOS or cigarette smoking in dual users.

This figure shows systemic nicotine exposure data in the U.S. REX study. Nicotine equivalence is on the y-axis and study days on the x-axis. The first 5 study days are product use in confinement, and then visits at 30, 60, and 90 days reflect use during the ambulatory period. The blue line represents the IQOS arm, the red line represents the cigarette arm, and the green line represents smoking abstinence. You can see the similarity between IQOS and cigarettes during the ambulatory period.

The REX and actual use studies reported the number of products used per day. With the exception of the confinement period in the REX studies, these are based on self-report, which is susceptible to missing and inaccurate data. These data are descriptive, and no statistical analysis was provided.

In the REX studies, there were small changes in the number of cigarettes and HeatSticks used per day. This figure shows consumption data from the U.S. REX study. The number of products used per day is on the y-axis, and the study day is on the x-axis. The first 5 study days reflect product use in confinement, and then visits at 30, 60, and 90 days reflect use during the ambulatory period. You can see the error bars are quite large.

In the actual use study, the combined number of products used per day showed a small decrease from about 10 cigarettes per day at baseline to 9 cigarettes and HeatSticks per day at Week 6.

Compliance refers to exclusive use rates of the IQOS system compared to dual use of IQOS and cigarettes. To match across studies, the data here focus on near-exclusive use where participants are using the IQOS HeatSticks at least 95% of the time that they smoke. These rates reflect the last month of the ambulatory period in the REX studies and Week 6 of the actual use study. The findings show evidence of dual use in participants with IQOS experience.

In the REX studies, for participants assigned to the IQOS arm, 85.9% of the Japanese sample was using IQOS nearly

exclusively. The U.S. study sample had a lower rate of near-exclusive use at 63.8%. In the actual use study, participants had a near-exclusive use rate of 7.5%.

There were some differences in study design that may affect consumption behavior. Participants in the REX studies received instructions to use their assigned product exclusively during the ambulatory period. Although participants were told they would not be removed from the study for use of other nicotine or tobacco product, noncompliance may be underreported.

Actual use study participants did not receive exclusive use instructions, so they were technically compliant. Moreover, they did not complete a monitored confinement period with exclusive IQOS use for 5 days. This may affect subsequent use behavior.

Smoking topography was measured in the REX studies. In the cigarette study arm, topography measures were generally stable over time. In the IQOS study arm, there were differences on a variety of topography metrics, including number of puffs, puff frequency, and smoking duration. The Applicant explains these differences as adaptation to the new product as it has differences in use properties as well as

nicotine delivery, flavor, and other characteristics.

Differences in behavior may also reflect topography measurement specifications of the IQOS holder and the study topography device. The IQOS holder limits smoking to a maximum of 14 puffs and 6 minutes of use. However, average number of puffs found in the study exceeded the 14-puff limit. This may be due to a higher measurement sensitivity by the study topography device compared to the IQOS holder. Alternately, the Applicant states that participants may overcome the 14-puff limit by using a technique that varies puff intensity.

Craving, withdrawal, and dependence were measured by self-report questionnaires. In the PK/PD studies, relief from craving was similar between IQOS and cigarettes over the 24-hour period. An example is shown in the top graph. These are within-subject data from the U.S. study showing QSU scores over 12 hours. The blue line represents the IQOS condition, and the red line represents the cigarettes condition.

In the REX studies, relief from craving and withdrawal were similar between IQOS and cigarette study arm. An example is shown in the bottom graph. These are data from three groups from the U.S. study showing QSU scores over 90 days. The blue line represents the IQOS arm, the red line represents the

cigarette arm, and the green line represents the smoking abstinence arm.

In two of the REX studies, dependence was measured with the FTND. Over the 90-day study period, there were no differences in changes to dependence severity between IQOS and cigarette study arms.

The questionnaires have some limitations. No information is provided regarding validation of the translated versions. Questionnaires were not modified to replace references to cigarettes with IQOS or HeatSticks, and no assessment of the relationship between subjective measures and behavior was provided.

Reinforcement was measured by the modified Cigarette Evaluation Questionnaire. In the single-use PK/PD studies, IQOS scored lower than own-brand cigarettes on all subscales except aversion with variability across studies.

In the REX studies, at the end of confinement, Day 5, the IQOS group had lower scores on all subscales except aversion with variability across studies. However, at the end of the ambulatory period, Day 90, there were no longer differences on any subscales between study arms. Limitations to the questionnaires were the same as those listed on the previous

slide.

In the actual use study, participants were asked about their likelihood to purchase IQOS if the IQOS device were available for $79.99 and a pack of Marlboro HeatSticks were available at a price comparable to a pack of Marlboro cigarettes. In the total sample set, approximately one-fifth of participants reported that they would buy IQOS. In a sample subset of participants that were using IQOS frequently by the end of the study, nearly half were willing to buy IQOS.

It is unclear if participants assumed that they had already owned the IQOS system and were being asked about buying HeatSticks only or if they were responding about buying both the IQOS system and the HeatSticks.

Data on product misuse, which may increase nicotine exposure and product use rates, was collected in the actual use study. IQOS misuse rates were low. Only 4.8% of participants reported using HeatSticks without the IQOS device. The majority lit the HeatSticks like a cigarette, and one participant chewed the HeatStick. Less than 1% of participants reported using the IQOS device without HeatSticks. One participant used the IQOS device with marijuana, and one used it with conventional cigarettes. Misuse may be underreported

because self-report data are susceptible to missing and inaccurate data.

Finally, to summarize the evidence to impact of IQOS use on tobacco users from a clinical and behavioral pharmacology perspective:

Systemic nicotine exposure was similar after single and multiple uses of HeatSticks and combusted cigarettes, both regular and menthol flavors. Nicotine exposures appear sufficient to provide user satisfaction.

IQOS use rates were similar to cigarettes. IQOS produces reinforcing effects and is expected to have an addiction potential that is similar to combusted cigarettes.

And now I invite Dr. Elena Mishina to join me in answering any clarifying questions.

DR. HUANG: Dr. Rees.

DR. REES: So you touched on topography, but you didn't give us any of the details on the puffing primaries. Were the data available? Puff volume?

DR. RASS: Sure.

DR. REES: Puff duration?

DR. RASS: I have some data available in front of me, but there is a lot of -- there were a lot of different topography

metrics, and there were differences in most of them. So there was variability found across studies and populations for both topography measures and adaptation rates to the new product, so the rate to reach stability in terms of topography metrics.

So compared to the cigarette smoking arm, participants in the IQOS arm took more puffs in three of four studies, they had a shorter smoking duration in two of four studies, they had a higher puff frequency in all four studies, and they did not differ in total puff volume. And there's a whole range of topography metrics that I don't have in front of me, but if you're interested, I could provide them.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: I think I know the answer to this, but if one wanted to decrease nicotine exposure, did any -- was there any data from these studies to suggest that IQOS would help reduce people's exposure to nicotine who used either IQOS or cigarettes?

DR. MISHINA: I don't think so. Nicotine exposure was very similar between both arms, and if there were a little bit differences in genetic mean values, it was corrected by population pharmacokinetic modeling of nicotine. When covariates as gender, menthol, ISO yield, cytochrome 2A6 and

1A2 were considered, then they are similar.

DR. RASS: And in these studies, participants did not have an intent to quit.

DR. HUANG: Dr. King.

DR. KING: So my comments -- I promise this is going to transform into a question by the end and relate to misuse.

And so I've been brought back to the standard for risk modification order, and if you look at the language, it's very carefully tortured, as we would expect from every respectable bureaucracy, as it's actually used by the consumer, and I think that's really key when we're talking about misuse. And you know, you can intend that they use it, but in this case, you know, there's certainly a degree of misuse. And looking at the percentages, it looks like 5%, at least, are misusing it, and I would disagree that that's low; that's actually pretty high. One in 20 people who are using the product are not using it correctly, and it's self-reported, in which case it's probably an underestimate of what's actually happening. And, of course, you know, we live in a population where apparently people are eating Tide Pods, so it's not surprising to me that we're having people chew the products as well.

But my question is how do we go about asking this in this

study and, you know, what -- how was it inquired and, you know, were they given directions how to use the product right? I presume they were just given the package and go with it, in which case that my expectation would be, in a real-world environment, as the user actually uses it, that it would be considerably higher, in which case 5% of misuse is pretty concerning from a public health perspective, when you look at 5% of the 40 million cigarette smokers that would presumably be using this product.

DR. RASS: All of the participants in the study prior to randomization were able to try the product, and I believe they were given a pamphlet on how to use it. I'm not sure if they were given specific instruction. And as to how to ask these questions, I would love to hear your opinion.

DR. KING: I have many opinions, but thank you.

DR. HUANG: Dr. Fagan.

DR. FAGAN: So Brian took care of my first question. My second question is, you know, as I reviewed the application with this definition of what people were provided, so the IQOS was provided free of charge and the cigarettes were not, and I didn't see any rationale for that. I think it's an important question because when we're designing trials, we're trying to

make sure we reduce as much bias as possible.

So did you see a rationale in the application related to why the cigarettes were not provided free of charge as well, because I didn't see it there. I'm just wondering if you guys saw something that I did not.

DR. RASS: I did not see a rationale. I believe -- products are also provided free of charge in the studies with the very low nicotine cigarettes. So that criticism would also apply there.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: Thank you, Mr. Chair.

I would ask, can the Committee be provided information on, in general, consumer products and misuse and what's an average, what's a high number? Because I don't know the answer to that.

MR. ZELLER: Within what period of time?

(Laughter.)

DR. McKINNEY: It's just in general. I think there was a statement made, and I just don't know in reference to other products, you know, is 5% high? I just don't know.

MR. ZELLER: We can try, but I don't know if we can do it in time for the deliberations of the Committee.

DR. McKINNEY: Thank you.

DR. HOLMAN: I mean, I can say for OTC drugs, it varies tremendously, and it depends on the drug product, the intent-to-use population. And you know, I think for drug products, the way FDA looks at it, it depends on the severity of consequences of the misuse to what's a sort of acceptable or tolerable degree or level of misuse. So I think it varies tremendously. I don't think there's a single number that we can provide that might extrapolate a bridge to this specific product.

DR. McKINNEY: Would FDA say that the misuse that was observed or reported here meets a certain severity level?

DR. HOLMAN: Not today we wouldn't. We'll let you know in a couple months. You know, I think it is a little surprising, I guess -- to me, at least -- that such a large number of participants in the actual use study do try to light the HeatSticks, you know, kind of treat them as a combusted Marlboro cigarette even though they are much different in dimensions than, you know, the Marlboro cigarettes that are on the market today.

So I guess that's sort of what I can say now. And certainly call our attention to something, I guess, that we didn't necessarily anticipate, but we're still evaluating that.

DR. HUANG: Dr. Rees.

DR. REES: I'm a little unclear as to the conclusion that the abuse liability of IQOS is similar to a conventional cigarette. You know, some outcomes are comparable, but the one that I'm particularly interested in, the modified cigarette questionnaire, the mCEQ, where ratings were lower for smoking satisfaction, enjoyment of respiratory tract sensation, psychological reward, and craving reduction. In general, if we ask people if they liked the product, it's a pretty good indication of the likelihood that that product will be adopted and used, and it seems that consumers in this study are saying that they prefer it less than the conventional product. And it also seems to suggest, to me, that it's -- it informs the reason why there's such a low complete adoption rate of IQOS compared to the conventional product.

So can you comment on the abuse liability? You know, in my view it needs to be comparable to a conventional cigarette if there is going to be any likelihood of complete switching.

DR. RASS: Sure. And there were decreased scores on different subscales in the mCEQ compared to own-brand cigarettes, which is not surprising after a single use and after 5 days of use, but in the two studies that looked out to

3 months of use, there were no longer differences. So presumably, people stick with it. It reaches a similar abuse liability based on that questionnaire.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Dovetailing on that question and what you just said, was any evaluation done to look at whether those subjective responses or patterns of use in the confinement period were related to retention in completing the study out to 90 days? Because if you're -- I would caution in making the assumption that, you know, people adjust to it over time; it could be that you're losing the people who didn't like it. And so the people who are retained out to 90 days are the people who made the initial adjustment, and you may not want to extrapolate back from 90 days to assume that all of those people eventually adjusted. Some of them might just have been lost because they didn't like it.

DR. RASS: So there were differences in the retention rate to the per-protocol population in the two 90-day studies. In the Japan study, I think it was almost all participants in the IQOS arm remained in the study, so that's one study that measured out to 90 days and found no differences. The U.S. study, I think the IQOS arm dropped by about half. But there

were no analyses over time to look more specifically.

DR. HUANG: Okay, Dr. Thrasher.

DR. THRASHER: Just one more question. In a number of places you raise potential issues with measurement, particularly with regard to the reference whether these abuse liability indicators are referring to cigarettes versus HeatSticks. Is there any sense that that measurement error matters with regard to the estimates here?

DR. RASS: I don't have a sense of that.

DR. HUANG: All right, thank you.

We'll move on to the next presentation.

Dr. Anic.

DR. ANIC: Good afternoon, my name is Dr. Gabriella Anic, and I'm an epidemiologist in the Center for Tobacco Products. I'm going to talk about evidence related to the impact on tobacco users and provide an evaluation of the epidemiological studies.

This is the standard disclaimer.

I'll first present an overview of the study design and results from four observational studies that provided data on IQOS use patterns among cigarette smokers.

The first premarket study is Perception and Behavior

Assessment Study Number 7, which was an actual use study conducted in the U.S. Dr. Rass just gave a brief overview of the study and talked about it in respect to the likelihood of participants purchasing IQOS and misusing the product. I will further discuss IQOS use patterns, including initiating IQOS use and switching from combusted cigarettes to IQOS.

The second premarket study is a whole offer test. This assessed IQOS use patterns in smokers in five countries in Asia and Europe. The Applicant also provided some preliminary results from two Japanese postmarket studies, including a cross-sectional survey of tobacco use patterns among smokers and nonsmokers and a survey of tobacco product use among individuals who had purchased IQOS.

Finally, I will discuss conclusions and some preliminary concerns that were identified during the review of these studies.

The first actual use study reviewed was the PBA-07 study, which was a longitudinal observational study that was conducted to assess near real-world IQOS use patterns among adult daily cigarette smokers. The study was conducted between September 2015 and January 2016 in eight cities. Participants were identified from a market research database that was comprised

of people who were interested in participating in research studies and were recruited from agency websites and referrals from friends and family.

Participants were required to be age 18 years and older, currently smoking cigarettes daily, and had no intention of quitting in the next 30 days. They must have also expressed a positive intention to use IQOS following exposure to IQOS marketing material. These materials included modified risk information, such as a statement that this significantly reduces the production of harmful and potentially harmful chemicals, and scientific studies have shown that switching completely from conventional cigarettes to IQOS system can reduce the risk of tobacco-related diseases.

To establish participants' baseline smoking patterns, they received an e-diary to record each time they smoked a combusted cigarette during a 1-week baseline period.

After baseline, participants received an IQOS device and regular or menthol HeatSticks free of charge. They then completed a 6-week observational period where they were instructed to use HeatSticks and any other tobacco products as they wished and were asked to record in their e-diary each time they used a combusted cigarette or a HeatStick.

Once a day, participants also recorded whether or not they used any nicotine replacement therapy, any e-cigarettes, or any other type of tobacco product, although they did not record the quantity that they used these products.

The second premarket study was a whole offer test, which is a series of longitudinal observational studies conducted to assess near real-world use of IQOS among daily cigarette smokers in Asia and Europe. The studies were conducted from 2013 to 2015 in Japan, South Korea, Italy, Germany, and Switzerland.

Eligibility criteria included being age 19 years or older, having smoked for at least 6 months, and smoking at least three cigarettes per day. Additionally, the Italy and Germany sites only included smokers of non-menthol cigarettes and the South Korea site only included men. All participants had to express a positive intention to use IQOS after trying a single HeatStick.

As was done in the U.S. study, participants were exposed to labeling and marketing material, although it is not clear from the protocol if these materials included reduced risk information.

At enrollment, participants were asked to report the

average number of combusted cigarettes they smoked per day to measure their baseline smoking patterns. The whole offer test did not have participants complete a 1-week baseline period as was done in the U.S. study. Participants were provided with a free IQOS device and HeatSticks and told to use the HeatSticks and any other tobacco products as they liked.

The observational period lasted 4 weeks where participants were asked to record in a paper and pencil diary each time they used a combusted cigarette or HeatStick. Use of e-cigarettes was collected in Italy and Japan only, and none of the study sites collected information on the use of other tobacco products.

Preliminary results from two postmarket studies conducted in Japan were also provided. IQOS became available for sale nationwide in Japan in the spring of 2016. A difference between the U.S. and Japan that should be mentioned which may influence the uptake of IQOS is that nicotine containing e-liquid is categorized as a pharmaceutical ingredient in Japan and is strictly controlled; therefore, nicotine containing e-cigarettes are not as readily available in Japan as they are in the U.S.

The first postmarket study was an online survey conducted

in September 2016 among 2,000 adults age 20 years and older who were recruited from an online research panel and included both cigarette smokers and nonsmokers. Participants reported their current use of combusted cigarettes, heat-not-burn products, and other tobacco products.

The second study was a survey conducted in a market research panel of adult IQOS purchasers age 21 years and older who purchased an IQOS device in the past 3 weeks and registered their device in an online database. Participants must have reported using at least 10 HeatSticks and/or combusted cigarettes per week. For the first 3 months, participants responded to weekly online surveys to collect data on their use patterns of IQOS and combusted cigarettes. After 4 months, participants completed online surveys on a monthly basis for up to 12 months.

Although the study was a longitudinal panel where participants completed surveys weekly or monthly, the study did not look at changes in individuals over time. Rather, during each month a new cohort of IQOS purchasers were recruited and added to the previously recruited samples to assess the prevalence of IQOS use patterns for that month.

This table presents results for three of the primary

outcomes in the premarket studies, including the prevalence of initiating IQOS use, switching from combusted cigarettes to IQOS, and switching from IQOS back to combusted cigarettes. The findings are grouped by geographic region to highlight the differences across countries.

At the end of the study, the prevalence of initiating IQOS use, which was defined as consuming at least 100 HeatSticks during the study, was lowest in the U.S. where 33.8% of participants met the 100 HeatStick threshold.

In the whole offer test, the proportion of participants who initiated IQOS use was highest in South Korea and Japan where 76% of participants in South Korea and 61 of participants in Japan used at least 100 HeatSticks. For the European countries, initiating IQOS use occurred in 50% of participants in Germany, 49% in Switzerland, and 36% in Italy.

Another primary outcome in these studies was switching from using combusted cigarettes to IQOS among participants who used at least 100 HeatSticks. Switching to IQOS was defined as HeatStick use accounting for at least 70% of the total number of combusted cigarettes and HeatSticks consumed in a week. It should be noted that this definition describes predominant IQOS use rather than complete switching.

In the last week of the U.S. study, about 33% of those who initiated IQOS use switched from combusted cigarettes to IQOS. In the whole offer test, switching to IQOS occurred most frequently in Japan and South Korea, where almost 50% of those who initiated IQOS use were classified as having switched to IQOS in the last week of the study. In the European countries, switching occurred in 18 to 37% of those who initiated using IQOS.

The studies also looked at the proportion of IQOS initiators who became exclusive IQOS users, which was defined more closely to complete switching, although it was not necessarily 100%, but it was defined as HeatSticks accounting for at least 95% of their total combusted cigarette plus HeatStick consumption in a week.

In the U.S., 16% of those who initiated IQOS were considered to be exclusive IQOS users during the last week of the study. The U.S. prevalence estimate of exclusive IQOS use was higher than what was observed in Europe but lower than what was seen in the Asian countries where exclusive IQOS use was around 20% of IQOS initiators.

Another outcome that was assessed was switching from IQOS back to predominantly using combusted cigarettes. A

participant was considered to have switched back to combusted cigarettes if HeatSticks accounted for less than 30% of their total combusted cigarette plus HeatStick consumption after having switched to IQOS in an earlier week. The prevalence of switching back to combusted cigarettes was highest in the U.S., where in the last week of the study about 15% of those who switched to IQOS had switched back to predominantly using combusted cigarettes. Switching back to combusted cigarettes was lowest in Asia where no participants switched back to cigarettes in Japan and only about 6% switched back to combusted cigarettes in South Korea.

This figure presents a proportion of participants in each of the main IQOS usage categories during the last week of the premarket studies by country. Unlike the previous table, this figure provides information about the prevalence of different levels of IQOS use among all cigarette smokers in these studies regardless of whether they were considered to have initiated IQOS use. Therefore, percentages for some usage categories will be different from what was presented in the last table.

In the U.S., indicated by the bar to the far left, the majority of people in the study were classified as predominant combusted cigarette users in the last week. This usage

category is denoted by the blue portion of the bar and accounts for 63% of participants in the U.S. study. About 22% of U.S. participants were considered combined users who reported HeatStick use comprised 30 to 70% of their total combusted cigarette plus HeatStick consumption; 77% of all U.S. participants were predominant HeatStick users, and 8% of all U.S. participants were considered exclusive HeatStick users.

In contrast, in Japan and South Korea, the prevalence of exclusive HeatStick use was 14 to 16%, about double what was observed in the U.S.

The U.S. actual use study assessed the change in the mean number of cigarettes smoked per day from baseline to Week 6 of the study. The figure shows the change in cigarettes smoked per day by IQOS use category at Week 6.

Daily combusted cigarette consumption decreased between baseline and Week 6 for all IQOS usage groups. The largest change was observed in the predominant IQOS use group where mean cigarettes smoked per day decreased from 9 at baseline to 1.4 at Week 6. The smallest change was seen in the predominant combusted cigarette user group where the mean number of combusted cigarettes used per day decreased from 10.9 to 8.3. However, it was not reported whether any of the changes in

cigarettes per day were statistically significant.

Across all groups there was minimal change between baseline cigarettes per day and mean total number of cigarettes plus HeatSticks consumed per day, indicated by the bars in red, suggesting that participants were replacing using cigarettes with HeatSticks rather than reducing their total tobacco product consumption.

In the Japanese postmarket study that assessed the prevalence of current use of various tobacco products, 71 participants, which accounted for 3.7% of respondents, reported that they currently used a heat-not-burn product with 96% of heat-not-burn product users reporting that IQOS was the product that they were using.

Dual use of heat-not-burn products with other tobacco products was common. Among current heat-not-burn product users, 91.8% reported that they currently used at least one other tobacco product, with cigarettes being the most common product used concurrently. Overall, 84.9% of heat-not-burn product users were currently smoking cigarettes with the majority smoking daily.

There was also a high prevalence of dual use with other tobacco products. About 59% of heat-not-burn product users

reported also using e-cigarettes, 38% were currently using smokeless tobacco pipes, 30% also used smokeless tobacco such as chewing tobacco, and about 25% also used cigars or pipes.

Another Japanese postmarket study was conducted among people who purchased IQOS and registered their device in an online database. Results were available from January to July of 2016. Dual use with other tobacco products was far less common in this population. The proportion of IQOS purchasers who reported exclusively using IQOS increased from 52% in January of 2016 to 65% in July of 2016. The prevalence of exclusive IQOS use was much higher in the survey than the premarket studies that observed about 8% exclusive IQOS use in the U.S. actual use study and about 14% exclusive IQOS use in the Japan site of the whole offer test.

In the application it was suggested that these discrepancies between the pre- and postmarket studies was due to increasing popularity and awareness of IQOS in Japan. However, it is also possible that people who took the initiative to register their IQOS device into a database are more highly motivated to become exclusive IQOS users and therefore may not be a representative sample of all users.

In summary, IQOS use patterns varied across the U.S.,

Asia, and Europe. In the U.S. study, about one-third of cigarette smokers initiated IQOS use, defined as using at least 100 HeatSticks. However, in the whole offer test, the prevalence of initiating IQOS use ranged from 36% in Italy to 76% in South Korea.

Dual use of IQOS and combusted cigarettes was common in all countries.

The prevalence of exclusive IQOS use was low in the U.S. with only about 8% of participants being classified as exclusive IQOS users during the last week of the study. In other countries, the prevalence of exclusive IQOS use ranged from 4% in Switzerland to about 16% in South Korea.

However, despite a high prevalence of incomplete switching, there was reduction in daily combusted cigarette consumption across all IQOS use groups in the U.S. study, even among people that were still predominantly using cigarettes at the end of the study, suggesting that IQOS users are likely to reduce their combusted cigarette consumption even if they continue to dual use.

Several concerns were identified in the review of the observational studies. First, we consistently saw that smokers who use IQOS become dual users. A concern is what effect dual

use of IQOS and combusted cigarettes compared to complete switching will have on reducing health risks for tobacco-related diseases and for reducing exposure to HPHCs. Epidemiological studies evaluating disease risk associated with reduction in smoking intensity have been inconsistent with regard to whether there is a significant reduction in disease or mortality risk associated with reducing cigarette consumption versus complete quitting.

Secondly, some features of the design of the actual use studies may impact behavior relative to real-world conditions. In these studies, participants received an IQOS device and unlimited HeatSticks for free. There is concern that some participants may have used HeatSticks to save money on cigarettes and would not have used the product if they had to make the initial investment of purchasing the device.

Another design feature to mention is the length of the observational period. IQOS used patterns -- use patterns, excuse me, were based on observational periods that span 4 to 6 weeks. It is unknown that these patterns will be sustained long term and whether additional smokers would switch from IQOS back to cigarettes if the follow-up time were longer.

The other design feature that should be mentioned is that

marketing and labeling material that participants were exposed to at enrollment contained modified risk information about reductions in disease risk and exposure to HPHCs. However, it is unclear whether participants noticed this information or whether this information impacted their patterns of IQOS use.

Finally, there is concern about how generalizable the results from the actual use studies are to U.S. smokers. The sample for the U.S. study was a non-probability sample that came from marketing research databases that recruited people by advertising and referral from friends and family. Therefore, the population is likely not representative of smokers in the general U.S. population. It is also unclear if results observed in other countries can be generalized to U.S. smokers.

The prevalence of initiating IQOS use and switching to IQOS varied across countries with these outcomes occurring almost twice as often in Asia compared to the U.S. These differences may be due to differences in cultural context or differences in the availability of e-cigarettes or other heat-not-burn products in these countries, such as Japan, where nicotine containing e-cigarettes are not as easily available as in the U.S. Therefore, it is unclear whether the findings from postmarket studies in Japan can be expected to occur among U.S.

smokers as a product that's to be marketed in the U.S.

Thank you, and I'll now take any clarifying questions.

DR. HUANG: Yes, Dr. Mermelstein.

DR. MERMELSTEIN: Thanks. I have a question about more the actual use study.

DR. ANIC: Um-hum.

DR. MERMELSTEIN: So in there, there are data about each time the participant used a product, they recorded it, right?

DR. ANIC: Yes.

DR. MERMELSTEIN: Okay. So are any of the situational analyses available to know when they used a combusted and when they used the IQOS so that we can see when, in the course of using it, first in the morning? That will tell us a lot about how they're using them and dual use and the satisfaction and reliability. Do we have that situational analysis?

DR. ANIC: That was not included in the application. I don't know if the data may be available, but that's not something that we looked at or had submitted to us.

DR. HUANG: Yes, Dr. McLoughlin.

DR. McLOUGHLIN: Somewhat related to what you were just asking, in these studies, do we have the idea of more of the demographics of exclusive use and predominant use folks? Like,

do we have a breakdown of which people ended up being the ones or characteristics of the people who ended up being --

DR. ANIC: We actually don't have that. I mean, we can request it if we find that we need to look at it. There were some analyses done by age and ethnicity and -- but it was to look at the primary outcome, so it's to look at initiation, not to look at switching. But I can't characterize the exclusive users versus the predominant cigarette users.

DR. McLOUGHLIN: Thank you. I just think it would be curious.

DR. HUANG: Dr. Mermelstein.

DR. MERMELSTEIN: Also, the data about the dual use or the poly use. So some of these participants use multiple products, tobacco products. They come into the study using those products, right? So are these people who are just more likely to be using lots of products anyway, and trying them? Do we know?

DR. ANIC: So we weren't provided with any data on the prevalence of the different product use at baseline, and again, we don't have data on how often they were using these products. So I don't know if the frequency of their product use changed. We just knew if they were using them or not throughout the

study.

DR. HUANG: Yeah. And so in the Japanese study, even though so many of them were classified as exclusive users, still almost all of them used some other product.

DR. ANIC: For the IQOS purchasers or for the other --

DR. HUANG: Because 91.8% --

DR. ANIC: Oh, okay, for the -- yeah, so the vast majority of them reported that they were currently using at least one other tobacco product.

DR. HUANG: Even though they're categorized as exclusive users, but they're in that high --

DR. ANIC: So that particular study didn't -- wasn't breaking down, like, IQOS usage categories; it was just whether or not they were using a heat-not-burn product and then if they were also using another tobacco product. So by those numbers, it would only mean that about 8% were only using heat-not-burn products.

DR. APELBERG: Just to clarify. Correct me if I'm wrong, but what you're talking about was a postmarket survey in Japan. That was just a survey of users, which --

DR. ANIC: Right.

DR. APELBERG: -- included IQOS users, you can see what

people were using. It wasn't the premarket, the whole offer test where they were assessing -- giving people the product and seeing what percentage switched or converted to the different categories.

DR. HUANG: Okay.

DR. ANIC: Right, yeah. IQOS wasn't the main focus of that, even though the vast majority of people who were using heat-not-burn products were using IQOS.

DR. HUANG: All right, thank you. Yes.

DR. BIERUT: I'm not sure if I'm understanding the studies correctly, but we do have some idea about people who are using IQOS. Do we have any idea who's going into a complete cessation where they're quitting both the IQOS and not going back into smoking?

DR. ANIC: We don't because we don't -- we actually don't have the numbers for how many people, like, were using 100% IQOS, so -- though we can request that information. But again, we don't get demographics for that exclusive IQOS category, so that 95 to 100% users, so I couldn't compare are they more likely to be women or older or younger compared to people who aren't making that switch to exclusive use.

DR. BIERUT: But these numbers in the post-surveillance

are getting quite large, and it would be interesting to see, you know, are people --

DR. ANIC: Yeah.

DR. BIERUT: Is anyone quitting.

DR. ANIC: Yeah, I suspect that there's differences between the populations of those -- that IQOS purchaser postmarket study and the premarket study, because there is such a vast difference in the proportion of people who are exclusive IQOS users, and we're still trying to wrap our head around why is there such a discrepancy between the premarket studies and the postmarket studies.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I just want to make a quick point, which is, in the studies just presented, we were talking about exclusive versus complete, and so the question that we have been asked to evaluate is about complete switching.

DR. ANIC: Right.

DR. FAGAN: So I just want to keep reminding the group -- well, everyone -- that the data before us are about exclusive, and I would like to see the data consistent across the different kinds of studies for the outcomes that Laura mentioned and for complete switching and if --

DR. ANIC: Um-hum.

DR. FAGAN: -- it's available, I think we need to see it because that's what we've been asked to look at.

The second question I had is do we have any idea, from the studies presented, what is the average number of HeatSticks used per day? Just curious. I mean, I don't know --

DR. ANIC: Yeah.

DR. FAGAN: -- if that's your data, but I'm just saying did you see it anywhere? I didn't.

DR. ANIC: Actually --

DR. FAGAN: I was curious.

DR. ANIC: -- that was not part of the tables that were submitted to us. We were focusing more on the usage categories, and we had data for cigarettes per day, but there wasn't a focus on the number of HeatSticks used per day, although they did provide, and I showed that in one of the graphs, the combination of how many HeatSticks and cigarettes were used per day.

DR. FAGAN: Yeah, that's a little different, but --

DR. ANIC: Yeah. Yeah, it is.

DR. FAGAN: -- thank you for that. Thanks.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Going back to that postmarket study as well, where you're looking at January, February, March, April.

DR. ANIC: Um-hum.

DR. O'CONNOR: What was the rationale given for looking at this in a repeat cross-section when you have a longitudinal design and you could look at how many people remain exclusive over those time periods? It seems a waste of the effort of creating a longitudinal panel.

DR. ANIC: Right. I cannot answer what the rationale was. It wasn't described in the protocol as to why it was designed exactly that way. And I agree, you do have this data to look at changes in individuals to see are they switching, are they sustaining their switching, but we aren't provided with that type of analysis.

DR. HUANG: Dr. Thrasher.

DR. THRASHER: Staying with the Japanese postmarket case with the people who are in the registry, you know, I wonder what the profile is of the people who are in the registry relative to the profile of combustible tobacco users in the Japanese population.

Is this really high-income, high-educated population, and so some intervention like this or permitting a product like

this into the marketplace may exacerbate health inequalities that are related to SES? I think that would be useful information to have, even though, as I mentioned earlier, I think the Japanese market is a lot different because they don't have legal e-cigarettes that are available without a prescription.

DR. ANIC: Right. Yeah, that again is information we also don't have, and what is the demographic distribution of this population to try to get a sense of how different is it from the general Japanese population and the general U.S. population.

DR. HUANG: Any other questions?

(No response.)

DR. HUANG: Okay, thank you. And we'll move on to the final FDA presentation.

Dr. Persoskie.

DR. PERSOSKIE: Hi, everybody. My name is Alex Persoskie, and I'm a social scientist in FDA's Center for Tobacco Products. I'll be giving an overview of the Applicant's proposed labels, labeling, and advertising materials, as well as the Applicant's research on smokers' and nonsmokers' responses to these materials.

Standard disclaimers.

My presentation will have two main parts: First, a description of the labels, labeling, and advertising materials. I'll refer to these as the LLA materials for short. Second, I'll give an overview of the Applicant's research evaluating these materials.

So, first, some background about how the Applicant proposes to inform consumers about IQOS. First, it proposes to use the LLA materials that it provided and studied in the applications. This includes an IQOS brochure, a HeatStick pack, and a direct mail communication.

Second, the Applicant proposes to communicate with consumers about IQOS using other methods. These may include print and digital ads, age-restricted digital and social media, and inserts and onserts on packs of conventional combusted cigarettes.

Finally, in other countries, the Applicant communicates with consumers about IQOS using smartphone apps and personnel in IQOS-branded stores, which we heard about from the Applicant this morning.

The LLA materials that the Applicant provided and studied in these applications contained three types of information:

descriptions of the product, modified risk claims, and either Surgeon General's warnings or statements that the Applicant developed that it calls PMI Important Warnings. I'll go over each of these in more detail on the next slides.

So, first, the descriptions of the product. The LLA materials in the application say that IQOS heats tobacco but doesn't burn it. The materials say HeatSticks have attributes that are similar to combusted cigarettes, like having real tobacco, having a filter, paper, a similar draw and number of puffs, and smooth tobacco flavor. These attributes could appeal to current smokers who have not switched to other electronic devices.

The materials also say IQOS has benefits over combusted cigarettes, like less odor, less mess, and no ash.

Finally, the materials have information on the intended and unintended users of IQOS. The intended users are said to be smokers who want to keep using tobacco.

Here are the Applicant's three modified risk claims that it studied on its LLA materials. The Applicant developed these claims in qualitative and quantitative research.

The first claim, in the left-hand column, says that the IQOS system heats tobacco but does not burn it, that this

significantly reduces the production of harmful and potentially harmful chemicals, and that scientific studies have shown that switching completely from conventional cigarettes to IQOS can reduce the risks of tobacco-related diseases. We call this Reduced Risk Claim 1.

The second claim in the middle column says, "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes." We call this Reduced Risk Claim 2.

Finally, the third column on the far right has the same first two bullets as Reduced Risk Claim 1, but the third bullet is different, saying that "Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals." We call this the Reduced Exposure Claim.

This slide shows Reduced Risk Claim 1 being displayed on one of the LLA materials; specifically, this is the brochure. This brochure had 20 panels, and these are the second and third panels.

This slide shows Reduced Risk Claim 2 on an unfolded HeatStick pack. There is also a statement labeled "Important Warning" on this particular version of the HeatStick pack,

which we'll discuss next.

The LLA materials included either Surgeon General's warnings for cigarettes or alternative statements that the Applicant developed which are labeled as important warnings. When Surgeon General's warnings were displayed, they were shown in a rotating fashion, just as they're shown on cigarettes now. We refer to the alternative statements that the Applicant tested as PMI Important Warnings because they all start with the words "Important Warning."

The Applicant proposed a different important warning for each of the three modified risk claims. Each important warning qualifies the content of its corresponding modified risk claim. So to briefly paraphrase, the statements that correspond to Reduced Risk Claims 1 and 2 say that the product still presents risk and that the best way to reduce risk is to completely quit tobacco use. They also say HeatSticks contain nicotine, which is addictive.

The statement that corresponds to the reduced exposure claim, in the right-hand column, is different. It contains some of the same information, but it first says that it has not been demonstrated that switching to IQOS reduces disease risk compared to conventional cigarettes.

Now I'll jump into Part 2 of the presentation, which describes the Applicant's research. Specifically, the Applicant submitted four studies assessing its LLA materials. With a few exceptions, the four studies all had the same methodology, including the study design, recruitment strategy, procedures, and measures.

The two exceptions were that the studies differed based on, number one, the geographic locations where the studies were conducted, and number two, whether or not the LLA materials had one of the three modified risk claims.

Here is a very high-level overview of the key aspects of the studies. I'll go over each of these areas in more detail in later slides, but I just want to give you a general framework for now because the rest of the presentation delves into the details of these studies and their results.

So starting at the top left quadrant, there were four studies. In one study, the LLA materials had none of the three modified risk claims. In the other three studies, the LLA materials contained one of the Applicant's three claims.

In each study, there were different conditions based on what type of LLA material participants viewed, as shown in the top right. Each study had five smoker groups, and each study

had four key outcomes, including risk perceptions, comprehension, intent to use IQOS, and intentions to quit smoking.

As mentioned, the four studies differed based on what claims were shown on the LLA materials. In Study NOC, on the left, the LLA materials didn't have any of the three modified risk claims. In Study RRC, the materials had Reduced Risk Claim 1. In Study RRC2, the materials had Reduced Risk Claim 2. And in Study REC, on the far right, the materials had the Reduced Exposure Claim.

Regarding study design, participants in each study were randomly assigned to view one of the three types of LLA materials, either the IQOS brochure, HeatStick pack, or direct mail communication. The materials had either Surgeon General or PMI Important Warnings, and the key outcomes were participants' perceptions of health and addiction risk from using IQOS and other tobacco products, comprehension of claims, intent to use IQOS, and intention to quit smoking.

Participants were all adults. In each study, they were recruited from four different cities with each city in a different one of the four U.S. census regions. Each study had a roughly equal number of people in five smoker groups,

including current smokers intending to quit, current smokers not intending to quit, former smokers, never smokers, and an over-sample of young adult never smokers. The Applicant studied its key outcomes separately in each of these smoker groups.

Participants completed the studies in person at research facilities. They completed the study themselves on a computer. After answering some initial questions, they were given hard copies of the LLA materials and they could view these throughout the rest of the study. One note about methodology is that in the studies where the materials contained one of the modified risk claims, there was no manipulation check to make sure participants noticed and read the claims.

Here are the different conditions in each study. Conditions differed based on what LLA materials participants viewed. In all the studies, participants viewed either a brochure, HeatStick packs, or direct mail.

In the claim studies, which are up top, the materials either had a Surgeon General's warning or a PMI warning.

In Study NOC, the no claim study, the materials always had Surgeon General's warnings. This means that in the conditions that are shown in blue on the slide, participants in the

different conditions viewed LLA materials that were similar except for the presence of the modified risk claims. So Study NOC can, in some sense, be thought of as a control where participants viewed similar materials but without the modified risk claims.

Here we show the four key outcomes and how they were measured. Perceived health and addiction risk were measured using a multi-item instrument that the Applicant developed and validated. These were assessed after participants viewed LLA materials.

Comprehension of the claims was measured using multiple-choice questions. The Applicant provided no information about the validity of its comprehension measures.

Intentions to try and use IQOS were assessed using single-item measures similar to those used in peer-reviewed tobacco research. Again, these were assessed after participants viewed LLA materials.

Intentions to quit smoking were assessed among smokers using standard items from peer-reviewed literature. Smokers reported their quit intentions before they viewed LLA materials. If they reported intending to quit, they were then asked again after viewing LLA materials to see if they still

reported intending to quit.

As far as analyses, the Applicant reported descriptive statistics for each outcome in each smoker group in each condition.

The Applicant also did follow-up analyses in which it compared key outcomes in the no claims study to outcomes in the claim studies. The purpose of this was to provide information about the potential effects of the modified risk claims.

So just as a reminder, the big picture here is that we have four LLA and claim assessment studies differing based on what modified risk claims were on the LLA materials. And we have the conditions that are shown here: these smoker groups and these key outcomes.

So now let's jump into the results. This is a figure showing how health risk perceptions looked in the no claim study. Specifically, this figure is from the brochure condition, but results were similar when people viewed a HeatStick pack or a direct mail. Scores can range from 0 to 100 with higher scores reflecting higher perceived health risk. The different colors represent different product types. Smoker groups are shown on the

x-axis. Let's focus on current smokers for now.

Smokers perceived a health risk of combusted cigarettes as highest, the red marks, followed by IQOS, the blue marks, and then

e-cigarettes, in yellow. Smokers perceived the health risks of these products all to above those of NRTs and cessation.

So what happens to smokers' perceived health risks when they view the LLA materials with one of the three modified risk claims? To provide information about this, the table at the top of this slide shows perceived health risks for IQOS in the claim studies compared to the no claim study. The table below that shows the results for combusted cigarettes minus IQOS, so in other words, the difference between perceived risk of combusted cigarettes and perceived risk of IQOS.

There were differences in both of these outcomes between the claim and no claim studies, which you can see by looking at the far right column of each table. As shown, smokers in the claim studies tended to perceive IQOS as somewhat lower in health risks compared to smokers in the no claim study, and smokers perceived a larger difference between combusted cigarettes and IQOS in the claim studies compared to the no claim study. Basically, this is what you would expect to see if viewing the modified risk claims reduced people's perceived

health risks of using IQOS.

This slide shows results on comprehension of reduced risk claims. In Studies RRC and RRC-2, comprehension questions asked about what would happen to smokers' disease risk if they switched to IQOS. Here we show the results and responses in Study RRC in the brochure conditions. We show results for all smoker groups together here.

The most common response was the one that PMI defined as correct, that complete switching can reduce smokers' risk of disease. The next most common response was that switching has the same disease risk as continuing to smoke, which was selected by almost a quarter of participants.

This slide shows comprehension results for the reduced exposure claim from Study REC. Specifically, a question assessed whether participants understood that switching to IQOS has not been demonstrated to reduce the risk of tobacco-related diseases. This table shows results in the brochure condition with the Surgeon General warnings versus the PMI Important Warning. Participants were much more likely to give the response defined as correct, shown in green, if they viewed the PMI Important Warning. Results were similar in the HeatStick pack conditions. However, note that even in the PMI warning

condition, 26% still said that IQOS reduces risk.

This slide shows results on smokers' intent to use IQOS in the no claim study. The upper table shows results on intentions to try IQOS. The table below that shows results on intentions to use IQOS regularly if one tries it and likes it.

In each table there is a column showing the percentage of smokers responding that they would very likely or definitely try or use IQOS. The Applicant calls this a positive intention. For your information, we also include a column showing the percentage responding somewhat likely.

The ranges in each of the table cells refer to conditions where people viewed either the brochure, HeatStick pack, or direct mail. As you can see, in both tables the intentions are quite high. However, we do note that participants were shown price information about IQOS and HeatSticks, but they did not actually have to make a choice between the product and money like they would have to do in the marketplace.

This table shows whether smokers' intent to use IQOS differed in the claim studies and the no claim study. As noted, the Applicant defined positive intentions as responding definitely or very likely.

This table has results for intentions to try and

intentions to use IQOS. As shown in the far right column, there was no consistent difference between the claim and no claim studies. In other words, smokers in the claim studies were no more likely to say that they'll definitely or very likely use IQOS than those in the no claim study.

However, we note that the Applicant only tested for differences in the likelihood of responding that one would definitely or very likely try or use IQOS. Dichotomizing variables in this way can reduce statistical power and bias results.

Here we describe smokers' intentions to quit smoking. In the no claim study, out of all the smokers who originally reported intending to quit smoking, between 1 and 14% no longer reported intending to quit after they viewed LLA materials. The comparable range in the claim studies was between 1 and 12%, so there's no evidence of a larger change in quit intentions when smokers viewed the LLA materials with versus without claims.

A couple of important notes on these findings: First, the changes in quit intentions may be because of low item reliability or testing effects.

Second, the Applicant did not reassess quit intentions

among smokers who originally reported not intending to quit; thus, the Applicant's research can't show whether the LLA materials may have stimulated quit intentions among smokers who initially did not intend to quit.

Now, let's look at results among nonsmokers. This figure shows how nonsmokers' health risk perceptions looked in the no claim study. This is from the brochure condition, but the same patterns held when participants viewed the HeatStick pack or the direct mail.

As we saw for current smokers, nonsmokers perceived the health risks of combusted cigarettes as highest followed by IQOS and then e-cigarettes. Also, nonsmokers perceived higher health risks of IQOS and other products than current smokers did.

So what happened when nonsmokers viewed LLA materials with one of the three claims? These tables provide information on this question. The first table shows nonsmokers perceived health risks of IQOS in the claim studies compared to the no claim study.

The second table shows the difference between perceived health risks of combusted cigarettes and perceived health risks of IQOS and how that differed in the claim versus no claim

studies.

Results are similar to what we saw before for current smokers. If you look in the first table in the far right column, you see that people in the claim studies tended to perceive IQOS as lower in health risk than did people in the no claim study.

In the second table, you see that people in the claim studies tended to perceive a bigger difference between IQOS and combusted cigarettes than did people in the no claim study.

This slide shows how perceived addiction risk looked in the no claim study. Specifically, this figure is from the brochure condition. As shown, nonsmokers perceived the addictiveness of combusted cigarettes as highest followed by IQOS and then e-cigarettes.

This slide shows comprehension results from Study RRC that may be especially relevant to nonsmokers. A comprehension question asked about the health effect of using IQOS. Across all smoker groups, 85 to 86% responded that using IQOS can harm your health. If you just look among the nonsmokers, this appeared even higher, 89 to 96%.

Finally, this slide shows results on nonsmokers' intent to use IQOS in the no claim study. Again, there are separate

tables for intentions to try IQOS and intentions to use it regularly, and there are separate columns for the percentages responding very likely or definitely and somewhat likely for each question. The ranges in each cell refer to different conditions where people viewed the brochure, HeatStick pack, or direct mail.

Overall, these percentages are much lower than what was observed for current smokers, which were all between 26 and 44%.

This slide shows whether nonsmokers' intent to use IQOS differed in the claim and no claim studies. The adjusted percentages are the percents responding definitely or very likely. As shown in the far right column, there was no consistent difference between the claim and no claim studies; in other words, no evidence that people in the claim studies were more likely to say they'll definitely or very likely try or use IQOS.

As a point of comparison for intent to use IQOS, the Applicant also measured nonsmokers' intent to use e-cigarettes. Just very briefly, nonsmokers' intent to use IQOS generally looked pretty similar to their intent to use e-cigarettes, or perhaps slightly lower, but the Applicant did not provide

statistical tests of these differences.

So to begin to wrap up. The LLA materials have information about IQOS, such as the intended users, the attributes that are similar to combusted cigarettes, potentially appealing to current smokers, and attributes that could be preferred over those of combusted cigarettes, like less odor and less mess.

Also, we note that IQOS has other features that may affect uptake among smokers and nonsmokers, such as a potentially high startup price, lack of flavors aside from menthol and tobacco, and the fact that all HeatSticks contain nicotine, unlike some e-cigarette products.

Regarding the modified risk claims, these provide information about complete switching. What the claims did not provide is information about the health effects of partial switching. This could be important if a lot of smokers only partially switch to IQOS and believe that they are decreasing their health risk or exposure to chemicals by doing so.

Here we summarize results on perceived risk. On average, smokers and nonsmokers both perceive IQOS as lower in health risk than combusted cigarettes and similar to or higher than e-cigarettes.

However, one very important note on these findings is that these were the results of average ratings of absolute risk. The studies did not ask people to directly compare the risk of using IQOS and combusted cigarettes.

We can't say for sure what those results would've been, but studies in the literature have found that when asked to make these direct comparisons between e-cigarettes and combusted cigarettes, a minority of U.S. adults believed e-cigarettes were less harmful than combusted cigarettes. Thus, our best guess, based on the literature, is that if they were asked directly, many U.S. adults would not perceive IQOS as less harmful than combusted cigarettes.

When smokers and nonsmokers viewed LLA materials with modified risk claims, they tended to rate IQOS as lower in health risk, and there was a bigger difference in the ratings of IQOS and the ratings of combusted cigarettes.

Regarding results on comprehension, the Applicant did not submit information on the validity of its comprehension items. This means that participants may have gotten the correct answer on some of these items simply by guessing.

Regarding comprehension of reduced risk claims, when people viewed the two reduced risk claims, most responded that

completely switching to IQOS reduces smokers' disease risk, and most also responded that IQOS can still harm your health.

Regarding comprehension to the reduced exposure claim, people's responses depended on whether they viewed the Surgeon General's warnings or the PMI Important Warning. When they viewed the PMI Important Warning, most people correctly responded that switching to IQOS has not been demonstrated to reduce a smoker's risk. However, about a quarter of participants still did respond that switching to IQOS reduces a smoker's risk.

Lastly, regarding intent to use products, smokers' intent to use IQOS was high regardless of whether they initially intended to quit smoking, and it was much higher than nonsmokers' intent to use IQOS. Most smokers who initially reported intending to quit smoking still did so after they viewed LLA materials and modified risk claims.

However, note that the Applicant did not assess whether intentions to quit smoking may have increased after smokers viewed LLA materials or modified risk claims. This would've been informative given that some smokers who currently don't want to quit could potentially change their mind if an acceptable alternative is offered.

There was some evidence of former smoker and never smoker intent to use IQOS. Specifically, intent to use IQOS in these groups looked generally similar to their intent to use e-cigarettes.

And lastly, the Applicant's analyses provided no evidence that the modified risk claims increased smokers' or nonsmokers' intent to use IQOS.

However, this may have been the result of how the Applicant analyzed its data, and we do expect downstream implications for product use if the claims change people's perception of the product.

Thank you, and I will now take clarifying questions if you have them.

DR. HUANG: Okay, Dr. O'Connor.

DR. O'CONNOR: So what I'm taking away from this is comparing the claim condition to the no claim condition, you get this slight decrease in people's perceived risk of IQOS relative to smoking, and that has no relationship to whether they intend to use the product. So this goes to something Dr. Bierut raised earlier is how are people interpreting that claim?

So earlier we heard the intention was for that to be

viewed as 50% or more reduction. If you look at the scale on which this is measured, you're getting about somewhere between a 3 and 6 point out of 100 reduction on their perceived risk scale, so that's far less than what the intended message is. And so I'm not surprised that that tiny reduction in risk, in perceived risk, is not associated with intention to use, so that begs the question, well, what's driving intention to use?

And, secondly, the other issue is, you know, perceived risk of cigarette smoking seems to be capped at around 80 on that 100-point scale, which makes me wonder what these people would perceive as riskier than smoking. So that raises some questions about the overall validity of that scale if cigarette smoking is not anchored near the top of it, especially in nonsmokers.

DR. PERSOSKIE: Yeah, I'd make a couple comments on that. First, I'd be careful as far as comparing effects on risk perceptions and effects on intent to use products. And also, before I even get into that, we should also be careful in terms of saying effects of the claims because, as I mentioned, people were not randomized to view the LLA materials with or without claims. Basically, the studies were conducted separately, although extremely similarly, so we can infer, you know, that

differences between the claim and no claim studies may be the result of the effect of the claims, but it's somewhat of an extrapolation.

But aside from that, my main point was the risk perception measures are measured very well in this application, you know, nicely developed and validated in multi-item measures, whereas the intention to use products, they're measured similarly to how they're looked at in the literature, like I mentioned.

But the Applicant wasn't able to build a multi-item scale that cohered in terms of psychometrics which, you know, when you use a multi-item measure, it tends to be more sensitive to -- you know, it tends to be a better measure, let's just say. So it's hard to say -- and I should also mention that the analyses of the intentions to use products weren't as good as the analyses of the risk perceptions because the -- as I mentioned, the analyses of intentions to use dichotomized the variable, so intentions to use were measured on a 6-point scale, and the Applicant only looked at changes in responses on the top two out of six categories. There could've been changes between 1 and 4 or between 5 and 6; we wouldn't know from their analyses.

So there are some caveats in saying that there were no

effects on intentions to use. It's quite possible that there were effects on intentions to use, and we do know from, you know, our own and published research on the link between risk perceptions and product use, that lower perceived risk of products is associated with a greater likelihood of using products cross-sectionally and longitudinally over time. So we do think that if the claims are changing risk perceptions, there are likely to be subsequent changes in product use.

DR. HUANG: Dr. Mermelstein.

DR. MERMELSTEIN: So then just a quick follow-up of what you just said, which is do we have, then, the data that shows the perceived risk -- intention to use by -- you know, on an individual level, by the perceived risk? You could say it's just been general, people are exposed to that as opposed to saying how does an individual's perception of risk relate to their intent to use. You said from the literature we know that, but how about these data?

DR. PERSOSKIE: So you're asking did they look at the --

DR. MERMELSTEIN: Yes.

DR. PERSOSKIE: -- length of statistical --

DR. MERMELSTEIN: Yeah.

DR. PERSOSKIE: -- association between risk perception and

intended use?

DR. MERMELSTEIN: Oh, the people who -- right, who had a certain risk perception you would anticipate.

DR. PERSOSKIE: There were no inferential statistics, statistical analyses of these studies submitted to us aside from the ones that I -- you know, the claim versus no claim comparisons. All the other analyses were descriptive, just showing, you know, percentages or --

DR. MERMELSTEIN: Right. It's not inferential. It could still be descriptive just like -- instead, it's just looking at different levels of perceived risk, what's the intention to use.

DR. HUANG: Dr. Thrasher.

DR. THRASHER: I don't know, Rich. Did you want to follow up on that? I'm going to shift the topic here.

DR. O'CONNOR: I just wanted to jump in on -- a related point is the other thing I noticed is they pooled all of the claim studies together. Did they present any data for each of the claims?

DR. PERSOSKIE: They originally presented all their descriptive statistics separately by the different studies. They submitted an amendment that contained those inferential --

those analyses you mentioned that were pooled, and they stated that the results were similar for each of the three claims, so that's why they pooled.

DR. O'CONNOR: Okay.

DR. PERSOSKIE: But they didn't submit the results for each individual claim.

DR. HUANG: And this may be something that we can follow up. I mean, we're going to have a more open discussion after, I think, this next break. Then we might re-ask about that.

DR. THRASHER: Yeah, I guess my question is with regard to the validity of the comprehension questions. You raised that earlier, and it seems like there are a number of issues there that compromise the validity of the comprehension assessment, including no comparisons with the control group or some other control. And as I understand it, the participants had the material in their hands while they're being asked about these -- this information.

So whether that counts as comprehension or good test taking and kind of flipping through the materials that you have in your hand in order to find the right response is something that I wonder about.

So do you think of their assessment as adequately

reflecting comprehension, as we are supposed to be evaluating that in our assessment here?

DR. PERSOSKIE: I'll put that question back to you all. You know, I would have liked to have seen some description of, you know, pre-testing or -- of the comprehension items or some attempt to validate them, you know, by putting them -- looking at associations between variables that comprehension should be associated with. But, yeah, that wasn't -- that information wasn't in the application, and there was no control group, like you mentioned, to look at whether people could just guess the answer to some of these comprehension items.

DR. THRASHER: I don't even know if it would be guessing if they have the material in their hands as well --

DR. PERSOSKIE: Yes. Yes, yes.

DR. THRASHER: -- they'd be able to find the right responses.

DR. PERSOSKIE: Yeah, right.

DR. THRASHER: I guess that's part of my question.

DR. PERSOSKIE: Yes. Very valid point.

DR. HUANG: Dr. Fagan.

DR. FAGAN: I'm going to follow up on this comprehension issue as well, but it's related to the claims themselves. So

was there any data that helped us to get an understanding of how the participants interpret the system itself?

Because if you look at the different claims, HeatStick is used, you know, IQOS system is used, and my question is what does that mean to the user because that is critically important. And going back to the issue of the questions that Dr. Rees asked about combustion, if you take the HeatStick alone and heat it outside of the system, you get combustion. That's what we heard earlier, that it can combust. So what do the users understand the system to be? Because the claims are saying that using the IQOS system can harm your health.

Do they understand that to mean the entire system itself, used as intended, or do users think that the HeatStick itself, you know, if you -- that it alone, you know, can increase harm or reduce harm? And I just want to know if we have any data about what users understand the system to mean.

DR. PERSOSKIE: Well, the Applicant did conduct, as I mentioned, qualitative research, but that was mainly geared toward sort of developing the claims and the LLA materials, and I don't think they asked questions about kind of what, in general, people thought the IQOS system -- I guess I'm a little bit unclear about what your question is, like do people

distinguish between the IQOS system and understand how that's different from a HeatStick or --

DR. FAGAN: Well, you know, the questions we're evaluating are partly about claims related to lower risk or harm, and unless the user is using the product as intended and the entire system, then the claim is not valid. And so I'm just trying to understand what the user -- if there was any data that they presented on what the user interprets the system to mean. It doesn't sound like that exists.

DR. PERSOSKIE: Not to my knowledge.

DR. FAGAN: Okay. I have another follow-up question, but I'll hold it for now.

DR. HUANG: Okay, sure.

Dr. Bierut.

DR. BIERUT: So is part of the concern that we heard that about 5% of individuals lights this little device like a cigarette, is my understanding from the previous presentation. And so is our concern that there may be a misperception that smoking that is still a decreased risk?

DR. FAGAN: It's a perception about what the risk -- what device we're attributing the risk to or reduced harm to. Is it the complete device itself or the stick?

And so what I'm trying to understand is when I, as a user, am looking at these different claims and I'm reading them, you know, am I interpreting that stick itself to be reduced harm, or is it the entire device that is the reduced harm? And I don't know what users are interpreting, I have no idea, because I'm just asking is there any data on that.

DR. RASS: Can I clarify? The lighting the HeatStick, I think most people that lit the HeatStick in that 5% only misused it once, and I think possibly one participant did it multiple times, so it's not constant misuse, as far as I'm aware.

DR. FAGAN: Well, I think it's irrespective of the data related to misuse, it's about how they interpret the claim, and that's a different issue.

DR. HUANG: We do have a question from Dr. Ossip on the phone.

DR. OSSIP: Yes, thank you.

So I'm hearing and agreeing with a lot of concerns just about these measures, in terms of the validity of the measures and how to interpret them, and so I want to pick up on a couple of things.

One is if you look at Slide 30 on comprehension of reduced

risk claim, the response options are unbalanced. This is not -- this is not the -- I can read it. Based on the information on the IQOS materials, what could be effects of using IQOS on your health: None, it is totally safe; it is completely unknown; it is more harmful than conventional cigarettes; it can harm your health; and don't know. And it can harm your health is 85 to 86% responded yes across the LLA materials. That, you know, kind of seems like the default answer so that with the -- I guess one question is, is this some sort of a standard scale? I think this is one that the Applicant created, but from the standpoint of survey design, it's an unbalanced set of response choices that pulls for the response of -- that's desirable for the study.

The second is on the intent to start measure among never smokers, and I think this is robust to the all claim studies as well. I think we need to put this in context that intent to start as measured by reading something on materials being presented, you know, kind of in isolation from the way they would be rolled out in actual application is interesting and informative, and assuming the measures were valid, which we have some questions about, you know, it is interesting to know and may be suggestive.

But having these in the context of the full range of marketing approaches that were identified by the Applicant may produce very different effects. So two things there. One is that I wonder if there are any data presented by the Applicant, I don't remember seeing that in the materials that we got, on countries where this is already -- the HeatSticks are already available and being marketed, if then they see different kinds of warnings in that sort of an environment, does that influence intent to quit or understanding of the claims?

And the second is that intent to use was -- rates were similar for the HeatSticks compared to e-cigarettes. And getting back to that adolescent issue, since we don't know, we don't really have data on adolescents, which is where most of the initiation occurs, you know, don't know if it's generalizable, but that's sort of the closest that we might have that might have some implications for what uptake might be among adolescents.

So I know there was a lot in there, but a couple things were just in terms of that Slide 36, the choices for the effects of using IQOS on your health, I just wanted to confirm that is -- that was 530. I wanted to confirm that that was designed by the Applicant. To me, looking at that, I think you

wouldn't have had to do much to get people to give that, what's viewed as the correct response. And then the second is just in terms of that intent to start in the claim studies, were there any data available on this methodology in the context of the product already being marketed, how the claims might be -- the reduced risk claims might be perceived in that context as opposed to in isolation, looking at particular material?

And then the third, obviously, was just a point about this seems something -- like something that -- the follow-up question is can you generalize that down to would that generalize to the adolescent population in terms of intent to use, uses similar to that for e-cigarettes?

DR. PERSOSKIE: So the comprehension items were, indeed, designed by the Applicant. I think that's sort of the nature of -- they had particular communication objectives, and they were very specific, so they kind of had to come up with their own comprehension items.

I did want to mention one thing about the measures. I don't want to trash all the measures that were used in the study because I think, out of the four key outcomes, you know, the risk perceptions, very defensible; intent to use products, very much consistent with what people would use in the tobacco

literature; intentions to quit smoking, also used in the literature. It's really the comprehension items that I would like to have seen more pre-testing in a control group or some evidence of validity for. The question you asked about the adolescents and whether results observed for intent to use, these products were generalized to adolescents, I think that's an interesting question because probably a lot of the Committee members know that whenever you deal with adolescents, often these types of questions are asked differently or scored differently, where researchers will basically take anyone who didn't respond that they'll definitely not use the product.

And if they say that they might use it, no, "somewhat likely," anything other than "definitely not," they'll classify those adolescents as susceptible, and it's been shown that those people who respond that way, the kids who respond that way are at higher risk of later trial and use of products.

DR. HUANG: And so I'd actually like to follow up on that with -- in Slide 31, where it is -- and I wanted to understand, in the NOC study, it's 7 to 10% of young adult never smokers were somewhat likely, then, to try IQOS, which is pretty concerningly high, and is that after they've been exposed to the messages?

DR. PERSOSKIE: No, these are from the no claim study.

DR. HUANG: But they get exposure, also, to the --

DR. PERSOSKIE: They were exposed to the LLA materials with no claims.

DR. HUANG: But no claims, okay.

DR. PERSOSKIE: And I should mention that this "very likely" or "definitely" categorization, this is something that was in the Applicant's protocol for the study, so they came up with this before they did the study. It wasn't a sort of a post hoc thing.

And their rationale for focusing on "very likely" or "definitely" and not including "somewhat" was that the marketing literature typically will focus on top two category responding, and I believe they even submitted a reference; it was sort of a best practices marketing paper that recommended top two categories.

The reason that we also include the "somewhat likely" category is that for some of the other studies that the Applicant conducted, I believe it was the actual use study, they had inclusion criteria for participants to, you know, take part in the study, and that criterion was that participants had to -- or potential participants had to respond "somewhat

likely," "very likely," or "definitely." So it seemed like they were defining things a little bit, you know, differently in that context; that's why we thought it would be of interest to present to you the "somewhat likely" responses.

DR. HUANG: So, I mean, actually then they had no claims that they were exposed to and it was just the Surgeon General warning.

DR. PERSOSKIE: Yeah.

DR. HUANG: And so they had that high of a "somewhat likely" inclination. You would think, then, if they were also exposed to the modified risk tobacco claim, they might be even more likely.

DR. PERSOSKIE: Yes, but there's no evidence that they were more likely to respond "very likely" or "definitely likely." Their analyses didn't look at change in "somewhat likely."

DR. HUANG: Okay. Dr. McKinney.

DR. McKINNEY: Thank you. We must have a list going over there.

DR. HUANG: I do have a list.

DR. McKINNEY: My question was related -- as you know, the industry is required to do these types of studies to answer

these questions, and you mentioned that these studies are consistent with what's in the literature. Are there any specific guidelines out there available, because it's a great conversation, but I know it's a nonclinical. In clinical, you know, you have ICH, OECD guidelines. Are there guidelines to instruct the industry on different ways or things they could've done differently with these studies?

DR. PERSOSKIE: I don't know of one place where they're all sort of together in one place. I know that one resource is the IOM report, Institute of Medicine report, that has some -- that has a chapter on study methods for consumer perception research on modified risk tobacco products.

We also always encourage a company who is thinking about submitting a modified risk tobacco product application to come and meet with us first. That way we can -- they can show us a protocol and information about how they're going to do their study, and then we can provide feedback on it and answer their questions.

DR. McKINNEY: Dr. Wanke.

DR. WANKE: All right, thank you.

My question is whether -- first, to confirm that all of these studies were done in IQOS-naive participants, is that

correct, that none of these were done in users?

DR. PERSOSKIE: Right, yes. These were done in the United States where IQOS was not on the market.

DR. WANKE: Okay, so there is no data on whether or not comprehension or risk perception would change after people have tried the system and would be interpreting these claims with that, having experienced the product? Is there any data?

DR. PERSOSKIE: If there were any of that evidence in the application, it would be in, like, say the actual use or whole market offer test, which I didn't review.

DR. WANKE: Okay.

DR. PERSOSKIE: I don't believe those studies had anything on claim interpretation or comprehension or anything of that nature.

DR. WANKE: And also just to confirm, this is only done with the non-menthol product? Packaging and labeling?

DR. PERSOSKIE: No. So if people were randomized to the HeatStick pack condition, if they were randomized to do a HeatStick pack, the HeatStick pack that they viewed was consistent with their preference for either menthol or regular.

DR. WANKE: Okay.

DR. PERSOSKIE: And that goes for former smokers as well;

they saw a pack that matched their preference.

DR. WANKE: But just the low or the high menthol condition, or did it compare the two? I guess it would just -- I guess they wouldn't -- I guess the participant wouldn't have an understanding of the difference in the level, so wouldn't be.

DR. PERSOSKIE: You mean the Smooth versus Fresh?

DR. WANKE: For Smooth versus Fresh, correct.

DR. PERSOSKIE: Yeah. I think there was just a 50/50 --

DR. WANKE: Okay. Thank you.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: So I'd like to go back to Dr. McKinney's question and also paraphrase something that Dr. Gilchrist said this morning. I do believe that you said that it was the policy of Philip Morris not to involve children under the age of 18 in these studies; do I have that correct? And we do know that the vast majority of cigarette smokers start before they're 18. I think that the mean age is 13. And I do believe that there are regulations that we're not allowed to target those under the age of 18 with advertising. I think I have all those comments correct.

So I think that we're talking about the wrong target

population at this point, the intent to try and intent to use. Without information on individuals under the age of 18, then we're aiming at a group that's at far less risk than those under the age of 18. I'd welcome pushback.

DR. PERSOSKIE: Well, just to chime in on that, for the question of switching and likelihood of current smokers switching to the product, I don't think it's correct to say that it's targeting the wrong population because presumably most of the switchers will be adult.

DR. WEITZMAN: Right, so intent to start using it or to try it? Do you disagree?

DR. PERSOSKIE: No, I mainly just wanted to point out that, in terms of the current smokers, the adults would --

DR. WEITZMAN: Right.

DR. PERSOSKIE: -- be preferable.

DR. WEITZMAN: That I agree with.

DR. HUANG: Dr. Thrasher.

DR. THRASHER: Robin, did you want to give a follow-on that?

DR. MERMELSTEIN: Well, just to address some of it. I think the young adult, the youngest of the young adult is very critical, and I think things have changed so dramatically in

terms of initiation patterns in the last few years that the young adults are the prize to look at.

And I also think that with changes in minimal legal age in lots of places, so I agree that that is, but I think we have to also be aware of who are -- you know, the changing patterns of whether people are initiating now, too.

DR. WEITZMAN: May I respond to that? I mean, if you look at Monitoring the Future and you look at the National Youth Tobacco Survey, it still is individuals under the age of 18 that one sees the steepest increase. In the e-cigarette users.

DR. MERMELSTEIN: E-cigs, yes.

DR. WEITZMAN: Right.

DR. HUANG: Dr. Thrasher.

DR. THRASHER: So going to this issue of e-cigarette use, I feel like we have an opportunity with this dataset to look at intentions to use e-cigarettes in these critical populations of never smokers and former smokers versus intentions to use IQOS and, you know, at the population level the means are about the same.

The question that I have is if you were to profile people who intend to use one product versus the other versus both, you know, is IQOS really appealing to a different population than

are being attracted by e-cigarette potentially? Because to me, that's a critical issue in trying to settle what's going on here in the context of the U.S. market where e-cigarettes are legal.

So does the Applicant provide any information showing us the profile of the people who intend to use the e-cigarettes versus the people who intend to use IQOS?

DR. PERSOSKIE: No, I don't believe they go into detail about intent to use e-cigarettes at all, sort of a contextual variable.

DR. THRASHER: So we just know the mean level is about the same, and it could be the exact same population.

DR. PERSOSKIE: And it's not mean levels; it's positive intent, you know, "very likely" or "definitely."

DR. THRASHER: Okay, so we're using those categories that they have. I think that information would be very useful.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Do you have a follow-up?

DR. McKINNEY: I have a follow-up.

DR. GIOVINO: Okay.

DR. HUANG: Okay, Dr. McKinney.

DR. McKINNEY: I had a follow-up for Dr. Weitzman. I

think that the population studied in these particular studies is appropriate. It doesn't invalidate what you're asking, and I think, if you recall, there was a postmarket surveillance program that was presented by Sarah Knakmuhs that addresses some of your concerns.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I have been struggling a bit with trying to understand what, on one level, is an inconsistency in all the verbiage you're presenting, the Applicant is presenting to people, and I'm just wondering -- I'm putting this out there, and I think I'll get to a question, but on the -- if you look at Slides 22 and 23, on Slide 22 the correct answer is next, thinking about all the information on the IQOS material, completely switching from conventional cigarettes to IQOS can reduce the risk of tobacco-related diseases. And on Slide 23, it says next, thinking about all of the information on the IQOS material, switching completely from conventional cigarettes to IQOS has not been demonstrated to reduce the risk of tobacco-related diseases.

Now, the more I think about this, the statement on Slide 23 is from a PMI warning, an important warning, and it's basically saying -- I think it's basically trying to say

reduced exposure does not necessarily mean reduced risk, and I think the Applicant is making -- trying to make the claim that well, you know, we really have lined up all of the steps in the pathophysiological process.

But you know what? Without the Applicant or without the respondent, the subject in the study, having those materials in his or her hands, he's not going to get that right 70% of the time, which is what the PMI warning is. So I think this stuff is just way too complex for the average Joe. And I'm thinking about studies with the food industry and, you know, people propose, like, the traffic light system, and the food industry sort of defaults to the complicated stuff, and I know it creates confusion among consumers. And I'm worried that this is an example, to me, of confusion among consumers.

I was on the IOM committee for the 2002 report, 2001 report, Clearing the Smoke, and we joked in that committee about a document we found -- Mike Cummings, I think, had found -- that at one point the industry debated pictographs with one dead rat, two dead rats, and three dead rats and, you know, never recommended that.

But the point is might there be a simpler pictographic way to communicate differential risk? And I'm wondering if the

Applicant went there at all in your read of their materials.

DR. PERSOSKIE: No, I believe, going back to the qualitative studies that I mentioned, I believe they started off with all textual claims and statements about product risk. I guess I totally see your point; it would be of interest to explore alternative ways of conveying information about product risk to consumers. But I guess the question for us would be overall are people better off, you know, just hypothetically, if IQOS was authorized to go on the market through a PMTA and had no risk information, no modified risk claims on it? Would people be better off in that situation or better off with the claims that they're -- or one of the claims that they're proposing here or some modified version of it?

DR. GIOVINO: Will the Applicant be able to market in stores, you know, like cigarettes, you can market cigarettes in stores now? Like, how will the Applicant reach consumers? Okay, direct mail marketing. Maybe this is a question more for later on. But, you know, to me there's so many ways this can be communicated, and right now, to me, this is just very confusing for the average Joe, I think.

DR. HUANG: And if I could follow up just -- on Slide 25, it does seem that the actual claims don't -- and I think

Dr. O'Connor mentioned, don't make that much difference in terms of the intentions to quit. I mean -- yeah. The language and whatever claims are being made, I think your summary at the beginning was it's not making that much impact on behavior.

(Off microphone comment.)

DR. HUANG: On intention to use.

(Off microphone comment.)

DR. HUANG: Right. But then also not intending to quit or intending to quit.

DR. PERSOSKIE: No, no, no, those refer to smokers who were not intending to quit or intended to quit.

DR. HUANG: Okay, that's -- okay.

DR. PERSOSKIE: But, again, there's caveats to this because, like I said, there's no evidence of changes in responding "definitely" or "very likely." If you took a means, you would have a more sensitive test of claims versus no claims because you would have a test of any change in responses versus just responding in two categories.

DR. HUANG: All right, I think we're going to take a break, and we still have time for -- opportunity for more discussion after that, so a 15-minute break. Again, Committee members, please remember that there must be no discussion of

the meeting topic either amongst yourselves, with the press, or with any member of the audience. Thank you. So we'll convene again in 15 minutes.

(Off the record at 4:40 p.m.)

(On the record at 5:00 p.m.)

DR. HUANG: All right, I think we'll go ahead and get started again. So our intention now, the intention is to end at 6:00. We are going to have another opportunity to ask, see if there are additional questions of PMI for a little bit, but then also have open discussion. So Committee members can be thinking about that use of our remaining time in that manner, a few additional questions for PMI and then also the opportunity for some open discussion.

Okay. So yes, Dr. Bailey.

DR. BAILEY: Questions for PMI. In looking at the tobacco that's in the IQOS product, some questions about the amount. I think it was in the literature about the amount of tobacco that's contained in the IQOS product as compared to a conventional cigarette.

And also I'm interested in types of tobacco that were used in that product. You mentioned flue cured, bright leaf, burley types you use in conventional cigarettes, but the types of

tobacco that are used in the reconstituted tobacco that's used in the IQOS product. I'm interested in how this product may impact U.S. tobacco production and growers here in the U.S. So just some questions about the sourcing of this tobacco, the types of tobacco, and the amount of tobacco, the volume used in this product compared to conventional cigarettes.

DR. GILCHRIST: It's U.S. tobacco in a smaller amount than in a cigarette, obviously, because the amount of tobacco in each HeatStick is around 300 mg, I think, Maurice? Yes, 300 mg compared to cigarette, which is about twice to three times that, if I recall correctly. So the amount of tobacco is smaller.

And nevertheless, what becomes extremely important with the tobacco that's used in the HeatSticks is the quality of the supply chain, so that becomes of paramount importance to ensure the consistency and reliability of the aerosol chemistry over time and through stick-to-stick comparison as well. So yeah, that's really of utmost importance.

DR. BAILEY: Okay, so what types of tobacco -- do you know what types of tobacco are used in this product?

DR. GILCHRIST: So we use similar tobaccos as are used in the range of our portfolio of conventional cigarettes that are

available, and of course, I can't go into specific quantities of each tobacco type because that's commercially confidential and -- but we're using typical tobaccos that we would use in cigarettes.

DR. BAILEY: Okay. And you said that some of this is coming from U.S. tobacco growers?

DR. GILCHRIST: That's correct, yes.

DR. BAILEY: Is that right?

DR. GILCHRIST: Yes.

DR. BAILEY: Okay. Any idea what proportion might be from the U.S.? Is that something you can share?

DR. GILCHRIST: Unfortunately, again, it's commercially confidential, but yes, it was U.S. tobacco in the HeatSticks.

DR. BAILEY: One thing I will add as far as the traceability of these crops of tobacco in terms of knowing how they've been grown, U.S. growers, really, that's really -- you know, you're going to have the most traceability from the U.S. growers versus offshore growers, and so I would encourage you to use more U.S.-grown tobacco in these products if you really want to have, you know, true traceability back to the grower and back to the procedures used to grow this crop.

DR. HUANG: I'd like to ask a question just to make sure I

understand some of your population effect calculations. So it's my understanding -- so if your estimates, if you are to get the MRTP designation, that the impact would be approximately 4,500 reduced deaths per year. I mean, for the product that kills about 480,000 per year in the U.S., your estimates are about 4,500 reduction per year; is that right?

DR. GILCHRIST: Right.

DR. HUANG: That's with the designation.

DR. GILCHRIST: Of course, we can't make a calculation per year; that's over the whole duration because, as Gizelle mentioned, some of the diseases obviously have a latency that will be affected by smoking, smoke pack, your history essentially. So we like to look at it over the full 20-year period, and the estimation, as I mentioned earlier this morning, was 90,000 lives that could be saved by bringing IQOS onto the market with its reduced risk claims.

DR. HUANG: Sure, but that would be distributed over that 20 years, so approximately something -- that is how -- what you estimate it to be. So I have a question, then. Have you done the calculations or considered -- so in Japan -- I mean, because also these calculations are based on completely switching to the product for current tobacco smokers, and so

you've got a lot of -- more data in Japan where there is more evidence of that. Have you done the calculations or considered, then, at some point moving all your product to this new product and what would be the impact on reductions in mortality or some of that population effect were you to do that?

DR. GILCHRIST: So that's the overall goal that we have over the long term is to transition all PMI's portfolio to a portfolio of potentially reduced risk products. Now, we have not modeled that in prospective models. As Gizelle mentioned this morning, the model is a counterfactual model, so it looked at a historical population. So I don't have data to share with you.

But certainly, the intention is that we move all our smokers onto a portfolio of potentially reduced risk products of which IQOS is the furthest forward in terms of our assessment. You've seen the amount of data that's in our application, and to our knowledge, that doesn't exist for any other product that's on the market today, including all of the electronic cigarettes that are available here in the United States. It simply is not the level of science that we have -- that we've put behind the IQOS product, and we're very excited

about the opportunity that that brings.

DR. HUANG: Yes, Dr. Weitzman.

DR. WEITZMAN: Please don't laugh, but in looking at all the documents provided by the FDA and by the industry, I don't know what IQOS means, what it stands for.

DR. GILCHRIST: Doesn't mean anything.

DR. WEITZMAN: Doesn't mean anything.

DR. GILCHRIST: No.

DR. WEITZMAN: It's not an acronym?

DR. GILCHRIST: No. In this day and age, it's very difficult to trademark a new word for naming a product, so you essentially end up with some random letters, and that's where we are. It doesn't stand for anything.

DR. HUANG: Yes, Dr. King.

DR. KING: So I'm interested, if you can speak to what your plans are to advertise these products. I did see, in the presentation given by Dr. Persoskie, that there was a summary of the intent to market by print and digital ads and also age-restricted digital social media channels, which I'm not sure what that means, maybe just pressing a button that says you're 18. But the reason I bring it up, because a lot of the marketing messaging was focused on brochures and mailers and

packs, but noticeably the internet was absent, and the internet, we know, particularly for e-cigarettes, is a prime venue for some of our inadvertent users, primarily youth. We know there's 18 million that are exposed to e-cigarette ads, and 10.5 of those are by the internet.

So I'm wondering if you can just briefly touch on what is the intent to advertise these products, and is the modified risk, the lower-risk message, going to be part of that internet advertising as well, outside of just the brochures, the mailers, and the packs?

DR. GILCHRIST: So Sarah from PM USA is the best person to answer that question, but what I would reiterate is that the regulations and therefore advertising restrictions that apply to IQOS, because it's classified as a cigarette, are quite different to the ones that are currently applied to electronic cigarettes. So, for example, television advertising would absolutely not be allowed for IQOS, whereas it is permissible for electronic cigarettes. But Sarah can give more detail about the --

DR. KING: But to clarify, internet would be, correct, so you could advertise by social media on there?

MS. KNAKMUHS: I'm going to take your question, if you

don't mind --

DR. KING: Yeah.

MS. KNAKMUHS: -- and break it into three pieces: First, provide a little bit more context, overall, of how we intend to market IQOS in the U.S.; second of all, look a little at how we intend to use the internet and perhaps social media; and then, third, just to make sure I specifically address where we plan on using the claim. Does that hit all your points?

DR. KING: You've got it; you're good.

MS. KNAKMUHS: Okay, great. Let's see if I can deliver on those. First of all, if we could show Slide 1. This is a broad-level approach at how we intend to market IQOS. Give us a second to get that popped up, okay.

This looks at a number of the different channels really focused around our three different approaches for marketing. Talked a little bit about awareness, making sure the consumer understands what is IQOS, what is the device versus the HeatSticks, what is heated tobacco versus burned -- versus traditional tobacco, some of the ways we're looking at doing that. We talked about some of them earlier today: direct mail, print media.

Second is trial. This is really important. This is where

we talked a little bit about having a guided trial. This gives the opportunity for a consumer to understand how do I put that HeatStick in, what's the right way to use it, how do I turn it on, how do I turn it off, and really making sure we don't have any misuse of the product. So that's second. We'll be doing that in one-on-one conversations, which make it very unique. Consumer events, we talked a little bit earlier about retail engagement.

Then the third way that we intend to market IQOS is through conversion, providing conversion support. This is having dedicated, high-touch customer care, so a consumer can call up, explain exactly what their issue is after they've been age-verified concerning on IQOS, providing personal support one-on-one. We know that consumers are going to have different problems based on their experience, so they can make sure that they get those answered.

So those are some of the -- our approach to marketing and some of the vehicles we intend on using to provide that information to the consumers in a one-on-one personalized way.

I'm going to switch to the second part of your question, unless there's follow-ups on that, around social media. Okay.

On social media, we know this is a new product, and we

know that we need new ways to communicate with consumers, so we're looking at using social media three different ways broadly.

First, customer care: Making it easier for a consumer that suddenly can't figure out how to turn it on or doesn't understand that their device isn't charged, providing customer care such as via Twitter. The goal there is to make it as easy as we can for a consumer to switch from cigarettes to IQOS.

We're also looking at doing dedicated branded webpages, marketing. What's important to note there is that we have a very extensive age verification process that the consumer will have to go to before they can get on the website. First, they have to verify they're a smoker. They have to independently verify their age; it will be verified by a third party so we can make sure the intended audience is getting access, for example, to our branded website.

DR. KING: So what's a third party, like a credit card company or what --

MS. KNAKMUHS: We actually use LexisNexis, which is deemed kind of to be the gold standard for age verification. So the consumer will enter their first name, their last name, their date of birth, if needed for verification purposes the last

four numbers of their Social Security number. It will get verified through LexisNexis; they'll be asked to answer verifying questions.

You know, we've all gone through this: What was your address 3 years ago, what was your job 6 years ago, those types of questions. They have that independent database to make sure that we're talking to the consumer so you don't have unintended audiences on that.

DR. KING: But isn't that something a child could enter for their own parent?

MS. KNAKMUHS: Well, a child could certainly probably enter their parent's name, maybe their birth date. I would query whether how many children know the last four Social Security numbers, some of the other questions that they'd be asked to answer. Possible, but we're doing everything that we can to limit that reach there. Yes?

DR. HUANG: Oh, okay. Is that a follow-up or --

DR. REES: It's a follow-up, yes.

DR. HUANG: Okay, Dr. Rees.

DR. REES: I'm interested in the use of social media, and I'm more interested in viral use of social media among adolescents. Certainly, smokeless tobacco products may not be

advertised electronically, but there are user groups of smokeless tobacco users that help to promote the use of tobacco -- smokeless tobacco products. We've certainly seen that with e-cigarettes.

It seems that IQOS is the kind of product that is amenable to precisely those sorts of strategies. How might you limit that, or what mechanisms might exist to limit that sort of viral gorilla marketing?

MS. KNAKMUHS: Certainly. And you're touching, actually, on our third way that we're looking at social media here, which is social listening. Our intent there is to get a better understanding of the consumer, making sure we're not seeing any unintended consequences popping up, for example, on the internet. If we do start to see any negative trends, we'll make sure to notify the FDA of those issues. We also actively monitor our trademarks and we'll -- as required to do so by the MSA, and if we see any issues, our trademarks being misused or that unintended audiences, we'll take the appropriate steps to limit that reach.

DR. HUANG: Follow-up? Dr. Mermelstein, just follow-up?

DR. MERMELSTEIN: Well, sort of a follow-up, but it's related to the marketing and the sales. People initially get a

package that contains the whole system, but then they need refills. So can you just purchase the HeatSticks without the device, and how long does the device last, and how does that happen? So people can just go into a store potentially and just get HeatSticks?

MS. KNAKMUHS: Sure, let me talk about -- kind of bifurcate that a bit. So there will be two different purchases that the consumer is going to have to go through. First, they're going to have to buy the device. We talked about earlier one place they'd buy the device, for example, is a dedicated retail store. They're going to have to go through an age verification process, confirming they're a smoker, going through that.

Once they've purchased that device, it lasts roughly a year. They will also have to make a separate purchase for the HeatSticks where they all go through the same sorts of age verification processes that they go through for traditional cigarettes here in the U.S., but we do believe, because it's the two age-verified purchases, that will also help to limit some of the unintended audiences having access to the IQOS system.

DR. HUANG: I do want to give Dr. Giovino a chance to --

or is yours a follow-up, direct follow-up or --

(Off microphone response.)

DR. HUANG: Okay, go ahead.

DR. GIOVINO: I'd like to ask -- go back to the health effects a bit. In the modeling, that lady who presented said -- that public health impact model, I think -- that population impact model that you had calculated relative risk for IQOS relative to Marlboros or, you know, Marlboro Reds or combusted cigarettes, I'm sorry. And so to what -- or maybe it was the opposite, but what were the ranges of estimates that you plugged in?

The National Academy of Medicine yesterday put out a report on electronic cigarettes, and David Mendez did the population models, and they were hugely dependent on, you know, how risky electronic cigarettes are compared to combusted cigarettes, and there was a range there. So I'm wondering what ranges, you know -- I know the lady who presented said relative risks, but whatever. What parameters were entered for comparative risk?

DR. GILCHRIST: So the advantage that we have for IQOS over electronic cigarettes is that we've done scientific studies on one single product. In the e-cigarette category,

there's been a range of products studied in multiple different types of studies, so I think that helps us to get a firm hold on what the type of relative risk would be for one single product versus smoking, so that was the focus.

Now, we looked at all of the studies that Manuel presented, and all the ones that he didn't unfortunately have time to present today, to come to the conclusion and create the assumption to enter into the model of the relative risk of switching completely to IQOS compared with continuing to smoke, which would be the alternative scenario.

And the assumption we made was that switching completely to IQOS brings with it 90% of the benefits of smoking cessation, so quitting altogether. So that was the assumption we made. But we also looked at more pessimistic scenarios just to be a little bit more pessimistic. So we looked at, for example, what would be the health benefits, population health effects, if IQOS were demonstrated over the long term to have only 70% of the benefits of smoking cessation, and even with that type of relative risk reduction, we still come to a very significant figure in terms of smoking-attributable deaths averted, and the figure was around about 70,000 versus the 90,000 with the 90%.

DR. GIOVINO: So, I mean, you know -- certainly, the chemistry, the biomarkers of exposure, those are all consistent with that. I want to raise the issue of the 23 of the 24 biomarkers of potential harm not being statistically different from the referent cigarette and, you know, how do you jive 70 to 90% with no biomarkers of potential harm, essentially 1 out of 24 being different?

DR. GILCHRIST: So Gizelle will come and help me with this answer, but we have to look at the evidence in its totality, and particularly that study, we also have to look not at differences of switching to IQOS compared to the continued cigarette use, but also looking at it in the context of what happened in smoking cessation, which is the gold standard for a smoker to reduce their risk. So we look at both comparisons compared to ongoing smoking but also what happened to the group who stopped smoking altogether, and Gizelle can explain the results.

DR. BAKER: So I think when we look at the study, we're talking about the reduced exposure study. The study was designed and powered to be able to demonstrate a reduction in exposure as compared to continued smoking. But in the study we also collected more secondary endpoints, the set of biomarkers

or clinical risk endpoints that could be called biomarkers of potential harm, some of which were expected to change, others which were not.

So we have all of that together in the study. And what we did and what we looked at was the changes that you see upon smoking cessation, and what you see upon smoking cessation are small changes that are not detectable within this study to be significantly different than that of continuing to smoke as well.

So all of this was put together, and what we know is that when you put this together with the cessation data, as well as the in vivo and the in vitro data, and you look at them after 3 months, what you would expect, what we saw from the clinical markers was that they all moved in the exact same direction as cessation, and they moved in similar magnitudes as what was seen upon cessation. And cessation itself is known to be linked to smoking -- reductions in risk of smoking-related disease; we felt this to be very important. And when we look at it overall, it's not just these markers on their own from this one study which would not allow us to conclude on the risk reduction potential by itself, but when we put this together in the context of all we saw on the mechanisms of disease, all the

endpoints across the different studies, the different biological systems, everything pointed in the same direction; it all pointed in the direction of risk reduction.

And so this was therefore able to allow us to make the conclusion when we took it together with the totality of evidence across everything, and that's where we went with the modeling. We used a Bayesian approach across all these endpoints to be able to look at how they compared to the cessation changes, not just how they compared to the smoking, and that's where we're able to come up with the different effects, the relative effective doses of the different products and the behaviors.

DR. GIOVINO: Thank you.

DR. HUANG: All right, Dr. Thrasher.

DR. THRASHER: Just a quick follow-up, sorry. I'm just looking at the tables, and you were just talking about how they all move in the same direction, and I don't see that when I look at these tables. In my handout it says Slide CC-57. And for inflammation, for example, switching to IQOS goes positive and abstinence goes negative, even though neither is statistically significant. So can you help me understand how that squares with what you just said?

DR. BAKER: So in the study with the -- in the U.S. study with inflammation, where we looked at the white blood cell, what we did see and what we presented in the overall package, the dossier, was when you look at the different time points.

So what we did see in that study is that there was a directional change in the same direction as cessation, but it was not bigger than what we saw with smoking, and what we actually saw in the 90-day endpoints with very -- at the very end of the study was that the change from smoking was actually larger than the change from IQOS, but both moved in the direction of cessation.

DR. THRASHER: Could you say that again?

DR. BAKER: Okay, let me try again.

DR. THRASHER: Just the last phrase.

DR. BAKER: When you look at Slide 57 and should I put -- should I put Slide 1 up, just go back to this? When you look at this, this is the effect of switching compared to continuing to smoke.

DR. THRASHER: Continuing to smoke.

DR. BAKER: So what you see was there was a decline in white blood cell count upon abstinence in the U.S. study and an increase compared to continuing to smoke in the IQOS arm. Both

of those, and actually all arms, had reduction in white blood cell count. So it was not as large as the reduction for smoking, but it was a reduction in white blood cell count, which is in the same direction as cessation.

DR. THRASHER: Now, this slide doesn't show anything about continuing to smoke.

DR. BAKER: This here is all the ratio, so this is the effect of abstinence compared to continuing to smoke, as well as the effect of IQOS compared to continuing to smoke. And what we see here is that smoking reduced the white blood cell count, as well as IQOS reduced the white blood cell count. So it was a positive difference between the two, but in essence, all of them moved in the same direction as what you would expect upon smoking cessation.

DR. HUANG: All right. Dr. Bierut.

DR. BIERUT: I have two questions. One is my understanding is there is some type of electronic device in this, and it is capturing data on the smoker; is that correct? Like how much they're puffing and their use?

DR. GILCHRIST: So we are able to capture data on, for example, number of puffs, number of sticks taken, but at the moment we don't implement that. The only time that it's ever

taken out of the device is if there's a failure in the device, if the device is sent back, for example, if there's some malfunction with a button or on. So we use it for diagnostic purposes, but we don't use the data for any other purpose.

DR. BIERUT: So you're not obtaining it in any other way. And then my second question actually is, you know, as I think of combustible cigarette smoking, it has caused tremendous harm with lung cancer, cardiovascular effects, COPD, but there is also mental health effects with combustible cigarette smoking. And there's growing evidence that there's a causation effect there also, and as we're moving to devices that hopefully reduce the physical harms, nonetheless, nicotine will remain going to the brain and can have effects, and are you planning to follow that or have any ideas about addressing this?

DR. GILCHRIST: So the focus of our application that's before the Committee today is on reducing the risk of smoking-related diseases, the main smoking-attributable diseases. So as I mentioned earlier, we focused on cardiovascular diseases, we focused on chronic obstructive pulmonary disease and lung cancer, which together make up more than three-quarters of all smoking-related diseases.

Now, in terms of mental health, we have not looked into

this, and we've not looked into the effect of nicotine on mental health. We do understand that there's a debate in the literature right now, but IQOS is not a product if you want to reduce your nicotine levels, if that was the direction you were going in. It delivers roughly the same levels of nicotine as a combustible cigarette, and we did that in order that smokers would find the product acceptable and be able to switch to it in order to reduce the risks of the smoking-attributable diseases that I just mentioned, so that was the focus of the application today.

DR. BIERUT: And so if we believe the evidence about nicotine causing the mental health effects -- again, I understand the model of you want the nicotine to make this transition to reduce the physical harms but not the CNS harms necessarily, and so those will likely remain.

DR. GILCHRIST: So the focus was on the major smoking-related diseases and on being able to provide a product that reduces the risk and evidence behind that.

Now, I understand that there is a debate about nicotine, but we do know from the literature that it's not the primary cause of smoking-related diseases, so the focus was on all the other harmful constituents that smokers are breathing every

single day when they're using combustible cigarettes. So our focus was on reducing those and providing smokers with an alternative today that can help them to reduce their health risk.

DR. HUANG: Mitch.

MR. ZELLER: I have a question about dual use and the countries where the product is currently marketed. Beyond explaining to consumers how to use the product and that the benefits will come from complete switching, what, if anything, has the company said or done in marketing in the face-to-face at the retail setting to explicitly take on dual use and the degree to which dual use would mitigate the positive effects of -- from complete switching in face-to-face or marketing materials for consumers in those other countries?

DR. GILCHRIST: So we understand the concern about dual use. I mean, the first thing I would say is that our studies that are part of the application have shown that there's no increase in tobacco use consumption during the day in consumers who dual used. But what we're focused on, as a company, is ensuring that we take that dual use as an opportunity to encourage the smoker to switch completely.

So we have run a number of programs in different countries

looking at different ways that we can help to encourage dual users to make the full switch and to do that in a shorter time frame as possible. So we've had coaching programs through mobile phones, we've had challenges to challenge the IQOS dual user to switch completely within a short period of time, and providing them with coaches that can help them through the natural adaptation period that we know that happens at the beginning when a smoker starts to switch.

MR. ZELLER: Just a follow-up question: So does that mean that you're explicitly sending a message to users, however you do that, about how dual use mitigates the benefits of the product?

DR. GILCHRIST: We explicitly send a message encouraging them to make the full switch to IQOS, the full switch. That's where we go.

DR. HUANG: Do you have a follow-up?

DR. REES: So that's interesting. Are those data available? What has been the impact of those interventions that you just described? And should we assume that the impact of those interventions are the data that we've seen here today?

DR. GILCHRIST: So they did not apply to the studies we did here in the United States. We cannot pull out what the

impact of those programs have had on the postmarket surveillance at this point in time from Japan, because it's too early, but we do see an increasing rate of complete switching over time in all of the countries where IQOS is marketed currently. And I think that shows our increasing ability to be able to communicate and help smokers to understand the importance of completely switching, and that's what we're very focused on.

DR. HUANG: And do you have a direct follow-up, Dr. Giovino?

DR. GIOVINO: So, you know, I'm a public health person, I'm not a company, but if I was running the program, I would warn consumers about the dangers of combusted cigarettes, all combusted cigarettes, made by your company and by every company. You wouldn't win a lot of friends with doing that, but is that strategy at all in your future plans?

DR. GILCHRIST: I can speak for Philip Morris International. We are using that strategy in some countries, and as we speak, and because we're fully focused on shifting our portfolio from combusted cigarettes to products like IQOS.

DR. GIOVINO: But you said you're encouraging complete switching. There's a big difference between that and -- I

think -- and some of the media that are out there about the real dangers of combusted tobacco products.

You know, I'll give an example of just -- years ago, Philip Morris put out a guide to quitting smoking. It looked like something academics would do. I used to show that guide and then show your -- the magazine that you used to distribute to -- you know, on your mailing list. The one was kind of dull paper; the other was all the glitz of all the really fancy magazines. You could switch them; IQOS could be all the glitz, and the combusted cigarettes could be the duller part of things. I realize these are sensitive issues, but I'm just wondering if, you know -- and there are lots of ways, other ways to communicate.

DR. GILCHRIST: I can just reassure you that our focus is on ensuring that smokers are accurately informed about the relative health risks of all tobacco products.

DR. GIOVINO: Sure.

DR. GILCHRIST: So that includes transparent information about the health risks of combustible cigarettes, but also, we hope, particularly here in the United States, having an ability to communicate to smokers the reasons why they should switch to a product like IQOS through the claims that we --

DR. GIOVINO: Sure.

DR. GILCHRIST: -- have applied for today and working to be able to do that as soon as possible because we know without IQOS people will simply continue to smoke.

DR. GIOVINO: So here's my concern. Decades ago, in the '50s, the cigarette companies warned people about -- they used a lot of words in their ads about we have filters, we have -- and then they were told to stop doing that, you know, when the health risks of smoking came out. And they stopped doing that, and they switched to words like smooth and light.

But now, for example, when Marlboro Ultra Light came out, it was pictures. You know, you're telling me all the cognitive rational reasons. Are you also going to use effective emotional marketing, is really what I'm wondering, marketing that appeals to feelings that can communicate differential risk in ways that aren't just cognitive rationale?

DR. GILCHRIST: So, of course, the statute created the pathway that resulted in the application that we made to the Agency at the end of last year and the reason that we're here today, and so we're very much limited by the application that we've made. I understand your ideas, and I think they're very interesting, but we have to stick with what we have, what we've

done in terms of an application, being able to work with the Agency on ways that we can effectively communicate the information in our claims to smokers in order that we can encourage them, give them the reasons why they should switch and encourage them to switch completely, which we believe the claims will help to do.

DR. GIOVINO: So marketing in convenience stores can't use images, or can it?

MS. KNAKMUHS: So I want to answer your last question but maybe provide a little additional context, too. So I'm with Philip Morris USA, which is a different company than Philip Morris International, just a quick point of clarification.

So our goal as a company is to be the leader in approved non-combustible reduced-harm products, and a critical part of that is for us to convert as many smokers as we can to IQOS and market that in the most effective way that we can. And your question on specifically at retail, yes, you're able to market that at traditional convenience stores as well.

And I would say, you know, another example to help show a level of commitment is we've talked about different ways that we're going to use the claim, how we're going to communicate to smokers about IQOS. But one that I always find particularly

compelling is one of the things we're looking at doing is taking a traditional pack of Marlboro cigarettes, on the outside of that packaging talking to that consumer about IQOS, letting them know about getting information there, directing them to a website where they can find out and start their journey on converting from cigarettes to IQOS.

DR. GIOVINO: Thank you, all.

DR. HUANG: Dr. Rees.

DR. REES: I'll just sort of follow up on that notion. Some years ago, when Philip Morris released the Marlboro snus product and I think in around about the same time Marlboro Ultra Smooth that were described as adjacency products, both were marketed as alternatives for Marlboros, smokers with the Marlboro branding. Do you consider IQOS an adjacency product?

DR. GILCHRIST: No, we do not. The IQOS product is an extremely important part of the future of both our companies, and we're delighted to be here today to discuss the merits of the science in our application, and we're looking forward to the Committee's deliberations and the ultimate decision of the FDA.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: Do you have any information on prenatal

effects or secondhand exposure to the aerosol? And if you don't, why don't you?

DR. GILCHRIST: We don't do studies in pregnant women because pregnant women shouldn't use nicotine or tobacco products at all, and that's the advice we give to them, and we have certainly no plans to be looking at the product in pregnant women.

DR. WEITZMAN: Right, but you haven't looked at adverse effects. It's the leading cause of low birth weight, of sudden infant death syndrome, of hospitalizations for asthma, tobacco uses, cigarette uses. So when you say you don't do work on prenatal use, don't you want to know whether or not it has negative effects?

DR. GILCHRIST: So the scientific literature shows that nicotine can have an impact on both the health of the mother and the health of the developing fetus, so our advice is that no pregnant woman should be using a nicotine or tobacco-containing product at all. They should consult their physician about the best approach for them. And certainly, we do not do studies on IQOS in pregnant women because it contains nicotine, it's addictive, and it's not risk free.

DR. KING: What about the second part of that question,

though, the secondhand aerosol? Yeah, could you address that, please?

DR. HUANG: Yeah, secondhand smoke, right.

DR. GILCHRIST: Yeah. So secondhand aerosol we have studied, and so we've done what we term indoor air quality studies where we've looked at the impact of using IQOS and combustible cigarettes in an indoor environment. So we measured a total of 19 different analytes, some of which were markers of environmental tobacco smoke and some of which were chosen because they were perhaps slightly less reduced in the IQOS aerosol versus combustible cigarettes.

In those studies, what we've been able to show is that when cigarettes are used in those environments, and we modeled all sorts of different environments like hotel, office, and residential environments, you can measure each and every one of those 19 constituents, analytes, at high levels in indoor air when combustible cigarettes are used.

On the contrary, when IQOS is used in that environment, we could only detect two analytes. The first was nicotine, so nicotine was detected in the air, which is to be expected because IQOS delivers nicotine. It was detected at levels that were, I think, 250 times below indoor air quality standards for

use of -- for detection of nicotine in a workplace, so 250 times lower, so extremely low levels.

The second compound that we detected was acetaldehyde. So acetaldehyde is present in the IQOS aerosol; it's also present in breath after you have alcohol and certain foods. So we measured that. It's very low levels compared to what was measured for combustible cigarettes, and it was about 40 times below the level that is mandated as the top level that's allowed for indoor air quality standards.

DR. WEITZMAN: May I follow up on that?

DR. HUANG: Yes, Dr. Weitzman.

DR. WEITZMAN: So has that been published in peer-reviewed journals? And when you say that the measures are that much lower, is that based upon the use of a single -- or how do you determine the dose of use of this that you're going to then measure in the house? But the peer-reviewed publication, to me, is extremely important.

DR. GILCHRIST: Yes. I'm just looking, it was published. Yes, yes. We can provide you with the reference.

DR. WEITZMAN: I would love that.

DR. GILCHRIST: Yes, absolutely. And so we followed a protocol, so we have a specially designed facility where we did

this study, and we followed a protocol whereby there were a certain number of smokers or IQOS users in the room, and they were asked to use a certain number of product over time, but it will all be detailed in the paper.

DR. HUANG: All right, Dr. Thrasher.

DR. THRASHER: I just have a quick question about the claims and then the PMI Important Warnings in the context of the claims. I'm wondering if you could help me understand how it is that you can, with the claims, say that scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risk of tobacco-related disease, while in your warning you say it has not been demonstrated that switching to IQOS system reduces the risk of tobacco-related disease compared to smoking conventional cigarettes. It seems to be saying two opposing things. Can you help me understand what you're trying to communicate by getting both those messages out?

DR. GILCHRIST: Right. Those messages were developed at different phases during the development and scientific assessment of IQOS. Now, as time has gone on, because we've gathered more evidence, more studies have been completed, and we've been able to draw conclusions from them. Our ability to

substantiate messages has increased over time.

So if you think about it, reduced exposure was something that we could demonstrate after the reduced exposure clinical studies, but some of the reduced risk evidence comes from complex animal studies, in vitro studies that haven't been completed.

So we believe that the evidence presented in our application supports all three claims, so risk reduction, harm reduction, and exposure reduction, but we developed the exposure reduction with the idea that potentially when we applied for the -- when we made the application, that we wouldn't have sufficient evidence to demonstrate risk reduction, which was why we added a disclaimer. But since then, obviously, we've developed much more evidence, but we included it in the package, and we have two alternatives, risk and harm reduced claims and exposure reduction claims.

DR. THRASHER: So then, really, that indication, the PMI warning that it has not been demonstrated, you wouldn't put that up as a message today?

DR. GILCHRIST: We believe that our evidence substantiates risk reduction, so in our view, it would not be necessary to disclaim the reduced exposure claim, if it was authorized by

the Agency.

DR. HUANG: And Dr. Giovino has a follow-up.

DR. GIOVINO: So you believe your evidence substantiates risk reduction in humans?

DR. GILCHRIST: Yes.

DR. GIOVINO: Okay. I'm an epidemiologist, and we study people in cohort studies and get data on people getting sick and dying, and the Surgeon General would never make a claim on that unless there was a substantial amount of biological data and human data. I know that we don't want to -- you know, we'd have to wait 30 years, so I totally understand that. But the claim that it can do this is that -- "can reduce risk" meaning -- does that mean it's possible to reduce risk? Does that mean, you know, there are steps in place to believe that it could do this in humans and some day we'll find out for real?

It's kind of -- I mean, when the first Surgeon General's report came out on cigarette smoking, it was cigarette smoking may make you sick, but they used the word "may," and this says "can," and the other ones say "presents." You know, the scientist in me understands that caveats are needed here, but I think I understand that you're trying to communicate something

that's a little clearer, but I'm struggling with that, to be perfectly honest.

DR. GILCHRIST: So I understand the point and the concern that you're making and, of course, epidemiology would be the best way to be able to quantify risk reduction and harm reduction in the long term, but of course, the downside is that we would have to wait, as you mentioned, 20 years for that evidence, and in the meantime, smokers will simply continue to smoke.

So the approach that we have taken is to look, as Manuel showed you, at the causal chain of events that goes all the way from being exposed to harmful constituents to suffering from disease and harm and look at evidence all across that causal chain to ensure that it was all coherent and cohesive, pointing in the right direction and showing very significant reductions compared to ongoing smoking and showing that it was coming close to the effects that are seen in smoking cessation, which is obviously the gold standard. So that was the approach we took because we know that the downside of waiting is that the product will not be on the market and we will not be able to inform smokers that it's a better choice than continuing to smoke, so that's why we took the totality of evidence approach.

DR. GIOVINO: Yeah. And I'm not asking you to wait. I'm wondering had you considered other words "may" or "likely" or --

DR. GILCHRIST: Yes. And Antonio can describe the approach that we took in developing the claims, which was quite comprehensive.

MR. RAMAZZOTTI: Yes, we have considered different wording for the claims. In fact, in all this process to come out with these three claims that we propose in the application today, we spent really a long time and considerable care.

In fact, we started with many different potential claims, even before going into research. Then we went into the very first qualitative research with nine messages to investigate. So what we learned, because we did alternate the "may" and "can," and what we learned from both smokers -- particularly smokers, in fact, is that "can" has a more affirmative value compared to "may," and therefore we decided to use "can" because, in fact, it is more aligned with the strength and the totality of the evidence that we have.

We also worked on this second message that you talked about, "presents less risk of harm," because, you know, we also wanted to evaluate and investigate different ways of

communicating the reduced risk profile of IQOS so that we could use them eventually, provided that they get approved, of course, affirmatively, to in fact convince about the need of complete switching.

And also what we learned in the same qualitative research is that for both smokers and nonsmokers, "presents less risk of harm," in fact, is equally understandable. It's a broader concept, but they consider it interchangeable between risk and harm and they consider harm linked to what is harm, harm to my health, harm to my health because I can get some diseases. So "it presents less risk of harm" was equally, I would say, adequate and appropriate.

DR. HUANG: And we will definitely have discussion of that tomorrow.

MR. RAMAZZOTTI: Yes.

DR. HUANG: I think Dr. Ossip on the phone has a question, if you'd like to.

DR. OSSIP: Yes, thanks. One advantage of waiting for a little while to ask a question is that a couple of my questions have already been asked, but I do have one other, and I'll start with the FDA, just trying to identify what's in our lane to be considering.

We've been focusing pretty much on smoke, for the most part, on current smokers switching to IQOS. I notice in our question, our list of questions to consider is the "evidence regarding the likelihood that persons who do not use tobacco products will start using the IQOS system," and we've seen the evidence presented from the studies done about never users looking at the labeling materials and identifying whether or not they'd start.

But my question for you is, is it in our lane to look at initiation per se, as well? So, you know, right now people are initiating using tobacco products. Are we looking just at current users switching to IQOS, or do we also expand that focus to people who are initiating tobacco use, initiating with something like an IQOS instead of a combustible tobacco product? And I say this because, you know, Dr. Gilchrist and others have said that the plan is really to shift the focus to these modified risk systems and, you know, if they're very successful and their goal is getting combustible tobacco users to switch in large numbers, at some point they'll run out, and that's not a sustainable business model, so what happens on the initiation end?

But before, you know -- so I had a few questions on that.

But before that, I just wanted to get clarification from the FDA. Is this in scope of what we're supposed to be considering at this meeting, or do we just stay with the current smokers switching, the question around that?

DR. APELBERG: Just to make sure I'm interpreting correctly, I'll go over sort of what we have laid out in terms of the questions specifically related to behavioral impacts. I mean, we essentially separated out, in Question 3, you know, really the assessment about, okay, this is, you know, a product that's intended to be marketed to current smokers. What do we think is going to happen with respect to use patterns there? And then Question 4 is intended to get at the initiation by nonusers, so you know, both a concern about youth, others who may take up the product who, you know, weren't intended to use it and for whom it wouldn't necessarily be a benefit but instead be a potential harm. So, I mean, that is what we intended to capture within the 4a and 4b. Does that make sense, or did I misinterpret?

DR. OSSIP: It does, but let me see if I can rephrase this. If this is approved as a modified risk tobacco product and is marketed, it won't be just visible to people who are switching from current tobacco products to others; it will be

viewed by others, and I wonder if it's part of the plan of the Applicant to encourage those who might otherwise be starting with combustible tobacco products to initiate with IQOS instead, either intentionally or as an unintended consequence, and that would have implications, perhaps good, perhaps bad, to go there. But that brings in that initiation issue; it broadens it a bit from what's been discussed so far today, from the results that were presented on those viewing labeling.

DR. APELBERG: Yeah. I mean, I think that Number 4, you know, before you get into the voting questions, it's really about a discussion regarding the likelihood that those who do not use tobacco products will start using the IQOS system. So, I mean, if the Committee members feel like the dynamics that you talked about are, you know, relevant and of importance in that context, for sure.

DR. HUANG: Because I know we've always felt that it falls under that charge, you know; the product as it's actually used by consumers would benefit the health of the population as a whole, and taking into account both users of tobacco products and persons who do not currently use tobacco products, so that has definitely been part of the discussion.

MR. ZELLER: The ultimate decision now is going to be the

Agency's, not the Committee's. It's going to be the Agency's job to make what you've heard us say is that -- sort of that net determination. What the Committee needs to grapple with, based upon the evidence that's before it, is embodied in the high/medium/low question on never users and likelihoods, and that's how you can inform the decision that we ultimately have to make. It's a net assessment. Separately, there's the opportunity for what needs to be -- were it to be authorized as an MRTP, what should be in postmarketing studies, surveillance, any other recommendations the Committee would have for the Agency in a scenario where there was a marketing authorization for a claim. But for now, it's what Ben described in Question 4, to inform our thinking in the decision that we ultimately have to make based upon the information before us, knowing that impact on never users is a mandatory consideration in the statute that we've put to you in the form of Question 4.

DR. GILCHRIST: Mr. Chairman, may I just address Dr. Ossip's concern about the business model for our company in the future?

DR. HUANG: Sure.

DR. GILCHRIST: So our focus is on the 40 million men and women here in the United States who currently smoke, and it

will take us many years to encourage them to switch to products like IQOS, but we will remain focused on that until we achieve it.

There's really no need for us to be looking to encourage unintended use because there is a large pool of smokers there that can provide us with opportunity for the foreseeable future. Our focus and goal here is to ensure that we're able to offer that product to those smokers and to provide them with information about why they should switch in order that we can shorten the time frame that it takes to switch the 40 million.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes, thank you. I have two separate questions, so I'm going to go back to your Slide Number 104, in the conversion block. And so just language clarification: The first part of your objective is to support exclusive or complete switching. I'm just clarifying; which is it?

DR. GILCHRIST: Complete switching.

DR. FAGAN: Okay, so we just need to make sure that that's noted. The second part is your example related to customer care and personal support, and there's an assumption that people will seek out customer care and personal support. Do you have -- and we know with that kind of support, you know,

there has to be some demand increase, some way of increasing demand for that.

Do you have any data from any of the other countries or that show what the rate is among users who use the customer care or personal support? I mean, just the demand for it among the current users.

MS. KNAKMUHS: So I'm going to turn it over to one of my colleagues, Antonio at PMI, to share a little bit about international learnings there, but I do think it's worth pointing out I provided some examples of where the consumer is affirmatively seeking out customer care. We're also looking at ways and supporting that conversion journey when we're reaching out to the consumer, someone who has registered via that database. We're providing them email reminding them what to do as well. So we're hoping that conversion support goes two ways, not just with the consumer seeking it out initially. And I'll turn it over to Antonio.

MR. RAMAZZOTTI: We do have strong evidence that, in fact, consumers who seek for customer care -- in Japan, we have received hundreds of thousands of calls with different questions. Now, I cannot quote the specific number because I didn't look into it, I may be able to ask between today and

tomorrow, if possible, to our Japanese colleagues.

But I can tell you that there are several hundreds of operators working just for IQOS in Japan to be able to answer questions, able to answer and address issues, problems. And this has been a very critical part of our marketing and customer care strategy in order to help consumers to make full switching by involving them for many issues with the device or help them overcoming questions that they may have with that.

DR. FAGAN: Okay, I think understanding the denominator is important. I mean, we know that about 1 to 2% of smokers call the quit line, so we should have a denominator for this customer care and personal support. Because even with e-cigarettes, we know that when e-cigarette users are seeking information about the devices, they -- it's a peer-to-peer kind of model, and we see that evidence in the vape forums on social media and so forth.

And so, you know, my question is -- just a question I'm speaking out loud, is what makes you think that they're going to come to the support care so that you can direct them towards complete switching versus them going to a peer-to-peer model, which we already have the evidence for with e-cigarettes? So it's just a question, and I have a second question. You don't

have to respond if you don't want to, but it just --

DR. GILCHRIST: I think there are a couple of critical elements that can help with that. First is labeling to instruct complete switching is, we think, vitally important. And then the second thing is ensuring that we have the correct postmarket surveillance, which, of course, is mandated under the statute and will be overseen by FDA to ensure that we have the right levels of switching, that we are driving smokers towards complete switching and not leaving them in a dual-use situation, and that will all be things that can be absolutely measured accurately in the postmarket setting. And we will use all the tools that we can to ensure that we're driving towards complete switching because that's our goal as a company.

DR. FAGAN: So I'm going to switch to a separate question, which is just going back to the question I asked some of the FDA scientists. What is the average sticks per day across the different studies? Did it vary by study, country? What do we know about the average number of HeatSticks used per day?

DR. GILCHRIST: So I think we have it broken out, certainly for the PBA studies and I think for the clinical studies. I'm not sure if we have an aggregate, but we could look to see if we could pull that together overnight. But

perhaps first, Antonio, you could speak to the PBA studies.

MR. RAMAZZOTTI: Yeah. In fact, we will check whether we can get this out for tomorrow, but I can show the data about the -- well, this has been asked also by Dr. Zeller earlier this morning, separating out the -- in the actual use study, the evidence of consumption and -- cigarette consumption between those who are exclusive, 95% or 100, versus those who are predominant. So if my team can find that slide, which has been very recently produced, hot off the press.

DR. FAGAN: And how do we know if, you know, fewer average sticks per day versus greater average sticks per day, how is that related to disease risk? I mean, I think it's an important question to think about. So you guys are going to have that as well?

(Off microphone response.)

DR. FAGAN: Okay, thank you.

MR. RAMAZZOTTI: Yeah. So let me finish addressing because we got the slide, Slide 1 up, please. And then eventually Gizelle can address the second part of the question. Slide 1 up, please.

So, Dr. Zeller, this addresses your question. On the left-hand side, you can see the usage and the change in usage

versus baseline among the group of exclusive -- 73. And on the right-hand side, you can see the difference versus those who used between 70 and 95%, the predominant. And, obviously, there is a slightly higher number of cigarettes consumed because they are less exclusive, but there is equal degrees versus baseline.

MR. ZELLER: Thank you. And I know that the *n* is starting to go down as we asked more and more clarifying questions, but -- so within the world of the 68 in the predominant use, which covers from 70 to 95% --

MR. RAMAZZOTTI: That's correct.

MR. ZELLER: -- can you slice that? What's it like at 70 and what's it like at 95? That was really my question.

MR. RAMAZZOTTI: Okay. We can look into it, and again, we can provide the data tomorrow.

MR. ZELLER: Thank you.

DR. HUANG: To follow, that slide, could you put that up again?

MR. RAMAZZOTTI: Can we have the slide back up?

DR. HUANG: Yeah. So the baseline, the number of cigarettes that they were smoking per day was just less than 10, less than half a pack?

MR. RAMAZZOTTI: Yes. On average, yes.

DR. HUANG: All right.

DR. FAGAN: Can you remind us, because each of these studies had different inclusion criteria for the actual -- and it was different for the REX study and actual use study and the WOT study. Can you remind us what the inclusion criteria were for the actual use study --

MR. RAMAZZOTTI: Sure.

DR. FAGAN: -- that allowed you to come to these data?

MR. RAMAZZOTTI: Sure. There had to be daily smokers, having smoked for at least 30 days or more and one cigarette per day at least.

UNIDENTIFIED SPEAKER: Excuse me. Wasn't there also a criterion that they were interested in using IQOS? At least somewhat interested?

MR. RAMAZZOTTI: Sure. That was also part of it, yes. I mean, there is more, and I can actually have Slide 2 up so that you can see all of them, so I was giving the short answer. So this gives you the full list of inclusion and exclusion criteria.

DR. OSSIP: And they were given the IQOS for free and no charge for HeatSticks?

MR. RAMAZZOTTI: They got access to IQOS for free.

DR. OSSIP: And that was whatever amount they requested?

MR. RAMAZZOTTI: There was whatever amount they requested, but we put in, in fact, in agreement with the FDA because when -- I remember we discussed this when we submitted the protocol. We put some limits so that they couldn't order more than a certain amount. If I recall correctly, they couldn't order more than double of their declared baseline consumption of cigarettes, but I think we never got to that limit, in fact.

DR. OSSIP: Okay, so that wouldn't have been a limiting factor in their use?

MR. RAMAZZOTTI: Yes.

DR. OSSIP: Okay, thank you.

MR. RAMAZZOTTI: Thank you.

DR. HUANG: I think we have one last question.

DR. BAKER: Clinical. So if we put Slide 1 up. Here you see the product use in the IQOS. You see the total consumption of IQOS per day, and then you also see, in the red bar, the consumption of cigarettes per day. So you see where they are at baseline, and you see the slight increase over time as they get to Day 90, in the per-protocol group.

(Off microphone comment.)

DR. BAKER: The yellow or orange is IQOS and that's the number of IQOS per day. And then when you look at the red bar, that's the CC arm, the comparator arm, and that's the number of cigarettes per day.

(Off microphone comment.)

DR. BAKER: Exactly.

(Off microphone comment.)

DR. BAKER: Yes, the first --

DR. BIERUT: Five days of confinement, but then the Day 30, 60, 90 is the ad lib, and is this everyone, or is this the people who were compliant?

DR. BAKER: This is the compliant group.

DR. BIERUT: And so what are the ends? What do you go from, because there 80 in IQOS, I believe, and how many remained compliant?

DR. BAKER: Forty-three.

DR. BIERUT: Okay.

DR. HUANG: Dr. McKinney.

DR. BAKER: And then I don't know if she still wanted me to answer the second question, which was the impact of product use on the reductions and exposure or potential link to harm.

DR. HUANG: Okay, sure.

DR. BAKER: So if you want to put Slide 3 up, and this one's probably a little more complicated, but I'll try and explain it. We looked at the people in the IQOS arm, at their number of products used in the upper, so those who are using the most products per day, how much they were using. So you see that the upper 25% of the IQOS users were using about 30 in the REX-C study, but when you go all the way out to the REX-A study on the far right, in the U.S. you see that the -- all users was very similar to that of cigarettes, but the top 25 were using more than the average population.

DR. FAGAN: Well, this answers a different question than the issue associated with HeatSticks per day.

DR. BAKER: And then I can carry that on to -- Slide 1 up -- to show what happens to the markers when you look at this. And what you see here is the light blue, the first bar in each of these markers, shows what happens for all IQOS users as compared to continuing to smoke. And what you see in the dark blue line is what happened in those upper 25% IQOS users, so the ones that were using definitely were IQOS. And then what you see in green is what happens upon cessation. And what you see between the light blue and the dark blue line is that the -- there's a little bit more exposure, but it's not

significantly larger.

DR. FAGAN: And did you take into consideration HeatSticks used per day with the data that you're showing here?

DR. BAKER: Yes. So this is what they're stratified by, so the people in the dark blue are using more HeatSticks per day. I think when you saw that last slide where I showed you the upper 25 percentile, they're the ones using -- 25 percentile of the population using the most IQOS per day.

DR. FAGAN: And tell us what that means, just in these -- what does that mean? The upper 25%, what range is that?

DR. BAKER: So, on average, they were using probably five to six sticks per day more than the overall population.

DR. FAGAN: Okay.

DR. HUANG: Okay, very last. Was there one final question that you had, Dr. McKinney?

(Off microphone response.)

DR. HUANG: We've got it covered? Okay. Unless there's any other compelling questions, I guess --

DR. FAGAN: Just one more.

DR. HUANG: One more, okay.

DR. FAGAN: Real quick. I just want to follow up on Dr. Weitzman's question earlier about the meaning of IQOS

because typically, in marketing, when you choose a name, a brand, a logo, it's pilot tested and you get feedback on it. And so can you explain to us how you came to that name?

DR. GILCHRIST: We had a huge list of hundreds of names, and we tested them with consumers to see which resonated, which conveyed technology, which was something that we wanted to convey in innovation, and we narrowed it down to IQOS.

DR. HUANG: All right.

(Off microphone comment.)

DR. HUANG: Pardon?

DR. GILCHRIST: I wish it were more glamorous than that, but it's not.

DR. HUANG: It seems like there would be more to that. Okay, is there anything else from your standpoint? So we apologize, we have definitely gone over, but I think we are adjourned for today. Tomorrow morning, what? We start at --

UNIDENTIFIED SPEAKER: Eight o'clock.

DR. HUANG: Eight o'clock. All right. Thank you all very much.

(Whereupon, at 6:10 p.m., the meeting was continued, to resume the next day, Thursday, January 25, 2018, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

January 24, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Tobacco Products.

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