

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEETING
(NDAC)

Wednesday, September 18, 2019

8:05 a.m. to 4:35 p.m.

FDA White Oak Campus
White Oak Conference Center
Building 31, The Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

1 **Meeting Roster**

2 **ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Cindy Chee, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS**

9 **(Voting)**

10 **Lorenzo Di Francesco, MD, FACP, FHM**

11 Professor of Medicine

12 Division of General Internal Medicine & Geriatrics

13 Emory University School of Medicine

14 Atlanta, Georgia

15

16 **Neil J. Farber, MD, FACP**

17 Professor Emeritus of Clinical Medicine

18 Division of General Internal Medicine

19 University of California, San Diego

20 La Jolla, California

21

22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Tonya S. King, PhD

Professor of Biostatistics
Department of Public Health Sciences
The Pennsylvania State University College of
Medicine
Hershey, Pennsylvania

Daniel L. Krinsky, MS, RPh

Owner and Pharmacist, EduCare4U, LLC
Co-Owner and Co-Founder, PGx101.com
Stow, Ohio

Pamela Mack-Brooks, MSN, RN, NEA-BC

(Consumer Representative)
Coordinator, Community Health Outreach Program
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

1 **Richard A. Neill, MD**

2 *(Chairperson)*

3 General Practitioner

4 Barraud Street Health Centre

5 Tararua Health Group

6 Dannevirke, New Zealand

7
8 **Maria C. Pruchnicki, PharmD, FCCP, BCPS, BCACP, CLS**

9 Associate Professor of Clinical Pharmacy

10 The Ohio State University College of Pharmacy

11 Columbus, Ohio

12
13 **Christianne L. Roumie, MD, MPH**

14 Associate Professor, Internal Medicine and

15 Pediatrics

16 Institute for Medicine and Public Health

17 Epidemiology Track Director

18 Master of Public Health Program

19 Vanderbilt University

20 Staff Physician, Veterans Affairs Tennessee

21 Valley Healthcare System

22 Nashville, Tennessee

1 **ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE**

2 **(Non-Voting)**

3 **Nora Zorich, MD, PhD**

4 (Acting Industry Representative)

5 Vice President (retired)

6 Research and Development

7 Procter and Gamble

8 Ann Arbor, Michigan

9
10 **TEMPORARY MEMBERS (Voting)**

11 **Susan J. Curry, PhD**

12 Dean Emerita and Distinguished Professor of

13 Health Management and Policy

14 College of Public Health

15 University of Iowa

16 Iowa City, Iowa

17
18 **Dorothy Hatsukami, PhD**

19 Professor Emeritus of Clinical Medicine

20 Division of General Internal Medicine

21 University of California, San Diego

22 La Jolla, California

1 **Suchitra Krishnan-Sarin, PhD**

2 Professor, Department of Psychiatry
3 Chair, Human Investigations Committee (IRB)
4 Yale University School of Medicine
5 New Haven, Connecticut

6

7 **David B. Nelson, MD, MSc, FAAP**

8 Chief, Division of General Pediatrics
9 MedStar Georgetown University Hospital
10 Professor of Pediatrics
11 Georgetown University Medical Center
12 Washington, District of Columbia

13

14 **Ruth Parker, MD**

15 Professor of Medicine, Pediatrics, and
16 Public Health
17 Senior Fellow, Center for Ethics
18 Emory University
19 Atlanta, Georgia

20

21

22

1 **Abigail B. Shoben, PhD**

2 Associate Professor

3 Division of Biostatistics

4 College of Public Health

5 The Ohio State University

6 Columbus, Ohio

7

8 **Jill Thomas, RMP, NMT**

9 *(Patient Representative)*

10 Westminster, Maryland

11

12 **FDA PARTICIPANTS (Non-Voting)**

13 **Theresa Michele, MD**

14 Director

15 Division of Nonprescription Drug Products

16 (DNDDP)

17 Office of Drug Evaluation IV (ODE IV)

18 Office of New Drugs (OND), CDER, FDA

19

20

21

22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Jenny Kelty, MD

Lead Medical Officer

DNDP, ODE IV, OND, CDER, FDA

David Petullo, MS

Statistics Team Leader

Division of Biometrics II

Office of Biostatistics

Office of Translational Sciences, CDER, FDA

Celia Winchell, MD

Lead Medical Officer

Division of Anesthesia, Analgesia, and

Addiction Products

Office of Drug Evaluation II (ODE II)

OND, CDER, FDA

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Richard Neill, MD	11
5	Conflict of Interest Statement	
6	Cindy Chee, PharmD	16
7	FDA Introductory Remarks	
8	Jenny Kelty, MD	19
9	Applicant Presentations - GlaxoSmithKline	
10	Introduction	
11	Sue James	29
12	Efficacy Review	
13	Mitchell Nides, PhD	39
14	Real-World Nicotine Replacement	
15	Therapy (NRT) Effectiveness	
16	John Hughes, MD	59
17	Safety Review	
18	Rajesh Mishra, MD, PhD	67
19	Consumer Studies Review	
20	Julie Aker, MT (ASCP)	79
21	Benefit-Risk Summary and Conclusion	
22	Sue James	87

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Clarifying Questions	93
4	FDA Presentations	
5	Efficacy and Safety Data in	
6	Clinical Trials	
7	Sarah Arnold, MD, MPH	112
8	Katherine Meaker, MS	117
9	Sarah Arnold, MD, MPH	124
10	Postmarketing Safety Data	
11	Martha Lenhart, MD, PhD	130
12	Label Comprehension Study	
13	Barbara Cohen, MPA	140
14	Clarifying Questions	152
15	Open Public Hearing	182
16	Clarifying Questions (continued)	202
17	FDA Charge to the Committee	
18	Theresa Michele, MD	239
19	Questions to the Committee and Discussion	245
20	Adjournment	335
21		
22		

P R O C E E D I N G S

(8:05 a.m.)

Call to Order

Introduction of Committee

1 DR. NEILL: Good morning, everybody. I would
2 first like to remind everyone to please silence your
3 cell phones, smartphones, and any other devices if
4 you've not already done so. I would also like to
5 identify the FDA press contact, Michael Felberbaum.

6 If you are present, please stand, Michael.

7 My name is Richard Neill. I'm the chairperson
8 of the Nonprescription Drugs Advisory Committee, and I
9 will be chairing this meeting. I will now call today's
10 Nonprescription Drugs Advisory Committee meeting to
11 order. We'll start by going around the table and
12 introducing yourselves. We'll start with the FDA to my
13 left and come around the table to the right.

14 DR. MICHELE: Good morning. My name is
15 Theresa Michele. I am the division director for
16 Nonprescription Drug Products.

17 DR. KELTY: Good morning. My name is Jenny
18 Kelty, and I'm a clinical team leader in the Division
19
20
21
22

1 of Nonprescription Drug Products.

2 DR. WINCHELL: I'm Celia Winchell. I'm the
3 medical team leader for addiction products in the
4 Division of Anesthesia, Analgesia, and Addiction
5 Products.

6 MR. PETULLO: David Petullo, statistics team
7 leader, Office of Biostatistics.

8 DR. HATSUKAMI: I'm Dorothy Hatsukami from the
9 University of Minnesota. I'm a professor of
10 psychiatry, and I do research on tobacco addiction.

11 DR. PARKER: Ruth Parker, general medicine,
12 Emory University, School of Medicine.

13 DR. ROUMIE: Christianne Roumie, internal
14 medicine and pediatrics; Vanderbilt university and the
15 Nashville VA.

16 DR. PRUCHNICKI: Maria Pruchnicki. I'm an
17 associate professor of pharmacy at the Ohio State
18 University in Columbus, Ohio.

19 DR. DI FRANCESCO: I'm Lorenzo Di Francesco.
20 I'm an internist and professor of medicine at Emory
21 university.

22 LCDR CHEE: Hi. Cindy Chee, acting designated

1 federal officer for the Nonprescription Drugs Advisory
2 Committee.

3 DR. NEILL: I'm Richard Neill. I'm a family
4 physician, most recently of the Tararua Health Group in
5 Dannevirke, New Zealand; currently homeless and
6 unemployed.

7 (Laughter.)

8 DR. KING: I'm Tonya King, professor of
9 biostatistics at Penn State College of Medicine.

10 DR. KRINSKY: Good morning. Dan Krinsky,
11 pharmacist from Stow, Ohio, independent consultant, and
12 visiting professor at Palm Beach Atlantic University.

13 DR. FARBER: Good morning. I'm Neil Farber,
14 professor emeritus at University of California San
15 Diego in the Division of General Internal Medicine.

16 MS. MACK-BROOKS: Good morning. I'm Pamela
17 Mack-Brooks, registered nurse, coordinator of the
18 Community Health Outreach Program at the Hospital of
19 the University of Pennsylvania in Philadelphia.

20 MS. THOMAS: Good morning. My name is Jill
21 Thomas. I am a neuromuscular therapist. I'm a brain
22 aneurysm survivor, and I've been nicotine free for six

1 years.

2 DR. NELSON: Good morning. I'm David Nelson,
3 and I'm a pediatrician epidemiologist in Department of
4 Pediatrics at Georgetown University.

5 DR. SHOBEEN: Good morning. I'm Abby Shoben.
6 I'm an associate professor of biostatistics at The Ohio
7 State University.

8 DR. CURRY: Hi. Sue Curry. I'm Dean Emeritus
9 of the College of Public Health at the University of
10 Iowa and still a professor of health management and
11 policy there.

12 DR. KRISHNAN-SARIN: Good morning. I'm
13 Suchitra Krishnan-Sarin. I'm a professor of psychiatry
14 at Yale University School of Medicine in New Haven.

15 DR. ZORICH: Good morning. I'm Nora Zorich.
16 I am the acting industry representative. I'm retired
17 from research and development at Procter and Gamble.

18 DR. NEILL: Nora, if you could turn off your
19 microphone.

20 Thank you and welcome to you all. For topics
21 such as those being discussed at today's meeting, there
22 are often a variety of opinions, some of which are

1 quite strongly held. Our goal is that today's meeting
2 will be a fair and open forum for discussion of these
3 issues and that individuals can express their views
4 without interruption. Thus, as a gentle reminder,
5 individuals will be allowed to speak into the record
6 only if recognized by the chairperson. We look forward
7 to a productive meeting.

8 In the spirit of the Federal Advisory
9 Committee Act and the Government in Sunshine Act, we
10 ask that the advisory committee members take care that
11 their conversations about the topic at hand take place
12 in the open forum of the meeting.

13 We are aware that members of the media are
14 anxious to speak with the FDA about these proceedings,
15 however, FDA will refrain from discussing the details
16 of this meeting with the media until its conclusion.
17 Also, the committee is reminded to please refrain from
18 discussing the meeting topic during breaks or lunch.
19 Thank you.

20 Now, I'll pass it to Lieutenant Commander
21 Cindy Chee, who will read the Conflict of Interest
22 Statement.

1 conflicts when it is determined that the agency's need
2 for a special government employee's services outweighs
3 his or her potential financial conflict of interest or
4 when the interest of a regular federal employee is not
5 so substantial as to be deemed likely to affect the
6 integrity of the service which the government may
7 expect from the employee.

8 Related to the discussions of today's meeting,
9 members and temporary voting members of this committee
10 have been screened for potential financial conflict of
11 interest of their own, as well as those imputed to
12 them, including those of their spouses or minor
13 children, and for purposes of 18 U.S.C. Section 208,
14 their employers. These interests may include
15 investments; consulting; expert witness testimony;
16 contracts, grants, CRADAS; teaching, speaking, writing;
17 patents and royalties; and primary employment.

18 Today's agenda involves discussion of data
19 submitted by GlaxoSmithKline Consumer Healthcare
20 Holdings, U.S., LLC to support new drug
21 application 208425 for over-the-counter marketing of
22 nicotine oral spray, 1 milligram per spray. The

1 proposed OTC use is to reduce withdrawal symptoms,
2 including nicotine craving associated with quitting
3 smoking.

4 The applicant has proposed to label the
5 product for adults 18 years and older. The committee
6 will be asked to consider whether data is supporting an
7 acceptable risk-benefit profile for the nonprescription
8 use of nicotine oral spray, 1 milligram per spray, by
9 OTC consumers.

10 This is a particular matters meeting during
11 which specific matters related to GlaxoSmithKline's NDA
12 will be discussed. Based on the agenda for today's
13 meeting and all financial interests reported by the
14 committee members and temporary voting members, no
15 conflict of interest waivers have been issued in
16 connection with this meeting. To ensure transparency,
17 we encourage all standing committee members and
18 temporary voting members to disclose any public
19 statements that they have made concerning the product
20 at issue.

21 With respect to FDA's invited industry
22 representative, we would like to disclose that Dr. Nora

1 Zorich is participating in this meeting as a nonvoting
2 industry representative, acting on behalf of regulated
3 industry. Dr. Zorich's role at this meeting is to
4 represent industry in general and not any particular
5 company.

6 We would like to remind members and temporary
7 voting members that if the discussions involve any
8 other products or firms not already on the agenda for
9 which an FDA participant has a personal or imputed
10 financial interest, the participants need to exclude
11 themselves from such involvement, and their exclusion
12 will be noted for the record. FDA encourages all other
13 participants to advise the committee of any financial
14 relationships that they may have with the firm at
15 issue. Thank you.

16 DR. NEILL: Thank you. We'll now proceed with
17 the FDA's introductory remarks from Dr. Jenny Kelty.

18 **FDA Introductory Remarks - Jenny Kelty**

19 DR. KELTY: Good morning. Dr. Neill, members
20 of the Nonprescription Drugs Advisory Committee, guest
21 members, our guests from GSK, and members of the
22 public, my name is Jenny Kelty, and I'm a lead medical

1 officer in the Division of the Nonprescription Drug
2 Products. On behalf of the division and all of us at
3 FDA, it is my pleasure to welcome you.

4 Before we get started, I wanted to thank the
5 members of the advisory committee who have taken time
6 out of their busy schedules to thoughtfully review the
7 briefing packages and be here today. Although this is
8 a nonprescription drugs advisory committee meeting, we
9 also have a number of guest members supplementing our
10 committee today. As guest members of the advisory
11 committee, you provide important expert scientific
12 advice that is taken very seriously by the FDA, and we
13 thank you for being here.

14 (Pause.)

15 DR. KELTY: We are here today to discuss the
16 new drug application for the over-the-counter, or OTC,
17 marketing of nicotine mouth spray, 1 milligram per
18 spray. Throughout the FDA briefing material and
19 presentations, we refer to the proposed product as
20 nicotine mouth spray or NMS. The objectives of today's
21 meeting are to discuss the efficacy and safety of
22 nicotine mouth spray for smoking cessation in the OTC

1 setting and to discuss the potential for abuse and
2 misuse of nicotine mouth spray.

3 Nicotine mouth spray is a solution containing
4 1 milligram of nicotine per spray. The solution is
5 sprayed directly into the mouth for oral mucosal
6 absorption. The proposed starting dose for adults 18
7 years of age and older is 1 to 2 sprays with a maximum
8 recommended dose of 4 sprays per hour and 64 sprays per
9 day. The proposed indication is for smoking cessation
10 and to reduce withdrawal symptoms, including nicotine
11 craving associated with quitting smoking.

12 Cigarette smoking cessation is a well-
13 established indication in the OTC setting, and the
14 proposed indication is the same as it is for all
15 currently approved OTC nicotine replacement therapy or
16 NRT products. Also, similar to currently approved oral
17 NRT products, the proposed product uses a 12-week quit
18 program divided into three steps.

19 However, unlike nicotine gum, for example, for
20 which the directions state to use one piece of gum
21 every 1 to 2 hours during step 1, then every 2 to
22 4 hours during step 2, and so on, the dosing regimen

1 for nicotine mouth spray is different in that the
2 directions do not include a fixed schedule.

3 For step 1, weeks 1 to 6, the directions are
4 to use 1 to 2 sprays whenever you would normally smoke
5 a cigarette or have a craving to smoke. Then for step
6 2, weeks 7 to 9, start reducing the number of sprays
7 per day. By week 9, you should be using half the
8 number of sprays per day that you used in step 1. Then
9 for step 3, weeks 10 to 12, continue reducing the
10 number of sprays per day so that you are not using more
11 than 4 sprays per day during week 12.

12 These are images of nicotine mouth spray in
13 its proposed packaging. As you can see here on the
14 right, there's a flap that opens up in the back Part
15 of the drug facts label, or DFL, is printed on the
16 front of the flap displaying the use and warnings
17 section.

18 The rest of the DFL, including the directions
19 for use, is revealed along with a quick start guide
20 upon opening the flap. This is a close-up of the
21 device in the front page of the user's guide that is
22 also included inside the product packaging. The user's

1 guide contains information about directions and
2 warnings as well as information on smoking cessation.

3 Currently, nicotine replacement therapy is
4 available over the counter as gum, lozenge, and patch
5 formulations. NRT gum and patch have been available
6 over the counter since 1996 and the lozenge since 2002.
7 Other NRT products such as the nicotine oral inhaler
8 and the nicotine nasal spray are available by
9 prescription only. Also, the non-NRT drugs bupropion
10 and varenicline are approved for prescription use.

11 As noted in the previous slide and as you can
12 see from this slide, nicotine mouth spray would be a
13 new dosage form of nicotine in the OTC setting. Other
14 unique characteristics compared to approved OTC NRT
15 products include its rapid systemic absorption of
16 nicotine, complex dosing directions, device component,
17 and discrete design.

18 In general, for any new drug that is reviewed
19 for OTC marketing, there are specific requirements that
20 are needed to be met. These are the benefits of the
21 drug must outweigh the risks. The potential for misuse
22 and abuse must be low. Consumers must be able to self-

1 diagnose the condition that is to be treated with the
2 drug. Also, the product must be able to be adequately
3 labeled within the OTC labeling requirements.

4 Labeling can be particularly challenging to
5 develop when the product has complex dosing directions
6 and can really make a difference in the OTC setting.
7 And finally, the product must be able to be used by the
8 consumer safely and effectively without the guidance of
9 a healthcare professional.

10 For NMS, because it is a new dosage form of
11 NRT that is proposed for direct to OTC marketing, FDA
12 requires that at least one efficacy study be conducted
13 in a simulated OTC setting. We refer to this type of
14 efficacy study as a real-world efficacy study. The
15 real-world efficacy study is intended to provide
16 evidence that consumers can use the drug product
17 effectively and safely, based on the label, without
18 assistance from a healthcare provider when they decide
19 to purchase it and take it home.

20 In a real-world efficacy study, subjects are
21 provided with a package containing the NRT drug product
22 with the planned drug facts label, or DFL, and any

1 self-help materials that are intended to be marketed
2 for the drug product. Also, study staff provide no
3 training and education on how to use the drug product,
4 and no additional behavioral support for smoking
5 cessation is provided by the study staff.

6 These last two points are very important
7 distinctions between a real-world efficacy study versus
8 a prescription drug study. Later this morning,
9 Dr. Arnold and Ms. Meaker from FDA will present the
10 results of the real-world efficacy study conducted for
11 NMS showing low continuous abstinence rates and a
12 treatment difference that was much smaller than in the
13 more controlled clinical efficacy study conducted under
14 prescription conditions.

15 This is a streamlined list of the highlights
16 of the NDA submission and the data that will be
17 presented and discussed today. For NMS, the OTC
18 clinical development program included two phase 3
19 safety and efficacy studies and one phase 3 terminated
20 study. One of the completed efficacy studies was a
21 real-world efficacy study conducted under OTC
22 conditions as described in the previous slide, and the

1 other one was conducted under prescription conditions.
2 The clinical development program also included 1
3 open-label pilot study and 4 clinical pharmacology
4 studies.

5 Also, due to the complex dosing directions and
6 the new delivery device, consumer studies were required
7 to demonstrate that consumers can understand the drug
8 facts label and use the device correctly; and in this
9 case, label comprehension and human factor studies were
10 conducted. The applicant also submitted a review of
11 the postmarketing safety data obtained from marketing
12 of the product in many countries outside the United
13 States, including the UK and Canada.

14 So getting back to our objectives for this
15 meeting, to support the discussions about the safety
16 and efficacy, we will be hearing presentations from GSK
17 and FDA about the two efficacy trials that had very
18 different results. The low continuous abstinence rates
19 and the small treatment difference in the real-world
20 efficacy study will be a main focus of our discussion
21 today. We'll be asking the committee members to
22 consider these different results and what they mean in

1 the overall assessment of efficacy of nicotine mouth
2 spray in the over-the-counter setting.

3 We'll also hear presentations about the label
4 comprehension study, and we would like the committee to
5 consider how consumer understanding of the drug facts
6 label and complex directions may impact the safe and
7 effective use in the real world where consumers would
8 use the product without the intervention of a
9 healthcare provider.

10 We'll also hear presentations about the safety
11 data from clinical trials as well as the various
12 postmarketing safety databases to inform the safety
13 discussions. Also, we'll hear a presentation about the
14 pharmacokinetic profile of nicotine mouth spray. The
15 rapid absorption of nicotine from nicotine mouth spray
16 when compared to nicotine lozenge is something to be
17 considered in the assessment of the potential for abuse
18 of this novel NRT for the treatment of smoking
19 cessation and the overall assessment of safety.

20 With that, I will conclude my introductory
21 remarks. We thank you again for your participation in
22 today's meeting, and we look forward to a productive

1 day.

2 DR. NEILL: Thank you, Dr. Kelty.

3 Both the Food and Drug Administration and the
4 public believe in a transparent process for information
5 gathering and decision making. To ensure such
6 transparency at the advisory committee meeting, FDA
7 believes that it is important to understand the context
8 of an individual's presentation. For this reason, FDA
9 encourages all participants, including the applicant's
10 non-employee presenters, to advise the committee of any
11 financial relationships that they may have with the
12 applicant such as consulting fees, travel expenses,
13 honoraria, and interest in a sponsor, including equity
14 interests and those based upon the outcome of the
15 meeting.

16 Likewise, FDA encourages you at the beginning
17 of your presentation to advise the committee if you do
18 not have any such financial relationships. If you
19 choose not to address this issue of financial
20 relationships at the beginning of your presentation, it
21 will not preclude you from speaking.

22 We will now proceed with GSK's presentation.

1 Ms. James?

2 **Applicant Presentation - Sue James**

3 MS. JAMES: Members of the FDA advisory
4 committee, good morning. I'm Sue James. I'm the
5 global head of regulatory affairs for GlaxoSmithKline
6 consumer healthcare. I'm joined today by my colleagues
7 at GSK, our invited expert speakers, and by
8 representatives of our development partner, Johnson &
9 Johnson or J&J.

10 We're grateful for the opportunity to discuss
11 our application for nicotine mouth spray 1 milligram.
12 This is a new product format for the U.S. intended as
13 an over-the-counter nicotine replacement therapy, or
14 NRT, to aid in smoking cessation for ages 18 and above.
15 The product is a solution of nicotine dispensed as a
16 metered dose of one milligram with a spray pattern
17 designed for buccal delivery.

18 Smoking cessation is important. In the U.S.,
19 cigarette smoking accounts for nearly half a million
20 deaths each year, more than HIV, illegal drugs,
21 alcohol, firearms, and motor vehicles combined. From
22 the 2015 National Health Interview Survey, many smokers

1 say they want to quit, 68 percent; 55 percent tried to
2 quit in the past year; and only 7 percent succeed, so
3 stopping smoking is hard.

4 Nicotine replacement therapy, or NRT, is a
5 first-line, evidence-based medication and the only
6 FDA-approved OTC drug to help smokers quit. NRT
7 products are well established as aids to smoking
8 cessation. There is substantial market history with
9 these products, and GSK has over two decades of
10 experience as leaders in this category.

11 The U.S. FDA first approved NRT as
12 prescription drugs in 1984, subsequently approving
13 Nicorette Gum and NicoDerm CQ patches for consumer
14 sales 12 years later in 1996. The increased access
15 associated with OTC availability resulted in a
16 significant increase in quit attempts, as I'll show on
17 the following slide. In 2002, FDA approved the last
18 new dosage form, which was oral lozenges. Product
19 improvements and FDA approvals since the original
20 launches include introduction of a consumer-preferred
21 clear patch, a mini lozenge, and most recently a coated
22 lozenge.

1 This figure shows, on the right, that in 1996
2 following the Rx to OTC switch of nicotine gum, in
3 purple and patch in orange, the estimated number of
4 quit attempts actually increased in relation to when
5 the products were available by prescription only, on
6 the left. We believe that continued innovation in this
7 category is crucial given the continued lethal
8 consequences of smoking.

9 FDA issued a call to action in 2017, holding a
10 series of public meetings, discussing a comprehensive
11 new tobacco policy and a commitment to increasing
12 access and youth of nicotine replacement therapy to
13 help more smokers quit. FDA encouraged further
14 innovation.

15 Discussions at these public meetings were
16 intended to build on the success of current NRT
17 products by looking at new ways to use NRT and
18 developing products that might address the relatively
19 slow systemic absorption of nicotine compared to the
20 nicotine from cigarette smoking.

21 The nicotine mouth spray, which we refer to as
22 NMS, is a new differentiated product form, which we

1 believe meets the challenge of innovation in this
2 category, with a nicotine absorption profile and a
3 dosing approach that is more flexible for consumers
4 based on their urge to smoke. The proposed indication,
5 like other NRT products, is to reduce withdrawal
6 symptoms, including nicotine craving associated with
7 quitting smoking.

8 This slide depicts the intended NMS product
9 presented as a spray canister in tamper-evident
10 packaging. To promote safety, the canister features a
11 locking and unlocking mechanism shown on the right of
12 the slide. This passes child-resistant testing
13 requirements. Inside the canister, we have a nicotine
14 solution that delivers 1 milligram of nicotine per
15 metered dose spray. To note, the spray patent droplet
16 size is designed for buccal delivery in contrast to the
17 pulmonary delivery of nicotine from cigarettes.

18 The nicotine mouth spray has over seven years
19 of market history outside the U.S. The spray was first
20 launched in the UK, Denmark, and Sweden in 2011. It is
21 currently marketed by our development partner J&J in 45
22 countries overall; and in 25 of these, it's available

1 as a self-selection product comparable to the OTC
2 access in the U.S. In the UK, Australia, and New
3 Zealand, the product is approved for adolescents age 12
4 and over. However, for the U.S., NMS is intended for
5 ages 18 and up.

6 In 2019, the FDA issued a draft guidance
7 document on the development of NRT drug products.
8 Although the NMS development program preceded this
9 guidance, it was built on several discussions with the
10 FDA and aligns nicely. The left panel summarizes the
11 FDA requirements for new products but differ from
12 currently approved conditions. In the case of NMS,
13 that would be dosage directions or usage directions.

14 Our development program included data from
15 pharmacokinetic studies and pharmacodynamic studies
16 specific for the innovation and also a 52-week efficacy
17 and safety study that we'll refer to as the Standard
18 study, a 26-week efficacy and safety study that we'll
19 refer to as the Naturalistic efficacy trial, and data
20 from label comprehension and human factors studies.

21 As it is presented as a solution, the buccal
22 absorption of nicotine from NMS is faster than other

1 NRT dosage forms. Time to reach maximum plasma
2 nicotine concentration is shorter, and concentrations
3 of nicotine are higher in the first minutes after
4 dosing. This results in more rapid therapeutic levels
5 of nicotine, which has a positive effect on the relief
6 from nicotine withdrawal symptoms, including cravings.
7 Dr. Mitch Nides will discuss the data from the PK and
8 PD studies conducted to characterize the profile of NMS
9 and how it compares to other forms of oral NRT, as well
10 as the nicotine delivery from cigarette smoking.

11 The safety profile of oral forms of NRT, such
12 as nicotine, gum, and lozenge, is well established and
13 favorable. There's extensive exposure to NMS from both
14 clinical trials and postmarketing experience from the
15 markets in which it's currently approved as a
16 nonprescription medicine. The NMS safety profile is
17 similar to other oral NRT, and Dr. Raj Mishra from J&J
18 will discuss the data later.

19 At the time of the U.S. nonprescription
20 approval of gums and patches in 1996, adolescent abuse
21 potential in the OTC setting was raised as a potential
22 issue. At that time, GSK undertook a phase 4

1 monitoring study for six years, which appeased that
2 concern. For the mouth spray, given the faster
3 reabsorption profile, we have considered whether abuse
4 might be a concern. We concluded that it is unlikely.
5 The absorption profile is lower and slower than inhaled
6 nicotine in cigarettes.

7 Our phase 4 data on gum and patch were
8 reassuring, and NMS postmarketing surveillance data
9 from ex-U.S. marketing does not show any new safety
10 signals. NMS would of course be subject to GSK
11 pharmacovigilance processes once approved with routine
12 safety monitoring, and as a new NDA, the product would
13 be subject to quarterly periodic reporting to the FDA.

14 I will now turn to the pivotal studies. Our
15 two pivotal trials demonstrated both the safety and
16 efficacy of the nicotine mouth spray. The first trial,
17 the Standard efficacy trial, was similar in design to
18 previous trials used to support the approval of current
19 NRT products. It included instruction and behavioral
20 counseling from trial staff.

21 The second trial, the Naturalistic trial, was
22 developed in concert with FDA. It was a different

1 design from our previous regulatory approval studies,
2 intentionally mimicking a worst-case scenario where
3 patients were introduced to the product with no
4 explanation of use or support by the study personnel.
5 Subjects had to rely on the label alone, and no verbal
6 counseling was provided at any point in the study.
7 Both studies met their primary endpoint of showing
8 significant differences from placebo.

9 Absolute quit rates were lower in the
10 Naturalistic trial, which we attribute to the design
11 and absence of verbal instruction or behavioral support
12 typically provided in smoking cessation studies.
13 Importantly, however, both trials demonstrated a
14 doubling of quit rate as generally seen with NRT.

15 Ensuring consumers can understand and use a
16 product appropriately is especially important in the
17 self-care setting. For NMS, the proposed drug facts
18 label and user's guide are based largely on the current
19 FDA-approved labeling for nicotine gum and lozenge.

20 The label refinement program focused on
21 statements unique to NMS such as the dosing directions
22 and instructions for operation of the dispenser. These

1 were generally well understood as well as the key
2 motivational messages within the user guide. Overall,
3 consumers demonstrated that they could use the device
4 based on the product labeling.

5 As with our current marketed NRT products, if
6 approved, GSK would market NMS along with a
7 comprehensive array of support materials to enhance
8 quit attempts. For the last 20 years, our products
9 have always included support materials, first
10 cassettes, then CDs, then a web-based committed
11 quitters program, which we have worked to enhance over
12 time.

13 NMS will be marketed with simple, engaging,
14 and user-friendly, self-help materials such as the
15 Quick Start Guide and User's Guide. Consumers will
16 also have access to online support, such as the newer
17 MyQuit Behavioral Support Program, demonstration videos
18 to help visualize how to use the product, and of
19 course, use of a 1-800 number for questions or comments
20 they may have.

21 For today's agenda, our first two speakers,
22 Dr. Nides and Dr. Hughes, are renowned smoking

1 cessation researchers with many years of clinical
2 experience. Dr. Mitch Nides will present the results
3 of the pharmacology program and pivotal efficacy
4 trials, demonstrating the effectiveness of the product
5 in achieving double quit rates. Dr. John Hughes will
6 provide much needed context of the results of our
7 pivotal safety and efficacy studies. He'll discuss
8 what is known from previous clinical investigations of
9 NRT as well as real-world experience.

10 Dr. Raj Mishra from J&J, our development
11 partner, will discuss the comprehensive safety data
12 available from clinical trials and extensive
13 postmarketing data from the 45 markets in which the
14 product is currently available as a nonprescription
15 product to speak to the overall favorable safety
16 profile.

17 Julie Aker from Concentrics Research will
18 present the outcome of our labeling studies that are
19 primarily focused on the labeling elements unique to
20 NMS, showing that, overall, consumers understand the
21 key elements of the labeling and can use the product
22 appropriately.

1 Lastly, I will return to summarize the overall
2 benefit-risk profile of the product and why we believe
3 nicotine mouth spray is an important innovation,
4 particularly at this time, offering a new medicinal
5 form of NRT to help consumers stop smoking. We also
6 have with us today a number of experts to assist us in
7 answering questions, and to note, all of our external
8 speakers and experts have been compensated for their
9 time and travel.

10 I will now hand over to Dr. Mitch Nides.

11 **Applicant Presentation - Mitchell Nides**

12 DR. NIDES: Thank you very much, Ms. James.

13 Welcome. My name is Mitchell Nides, and it's
14 really a great honor and a privilege to be here today.
15 Before I begin, as my disclosure, I have received, as
16 Ms. James said, compensation for time and travel. I do
17 not have any other financial conflicts with either GSK
18 or J&J. But over the past several years, I've
19 conducted clinical trials for and received consulting
20 fees from manufacturers of smoking cessation and from
21 alternative nicotine products.

22 My background is in clinical psychology and

1 research psychology. As president of Los Angeles
2 clinical trials, I've been the principal investigator
3 of over 50 smoking cessation studies over the past 25
4 years, including all forms of NRT as well as bupropion
5 and varenicline. I was also the lead investigator of
6 the nicotine mouth spray U.S. trial and the first
7 author of the publication.

8 I'm also the director of Picture Quitting, the
9 entertainment industry's quit smoking program. Our
10 program was initially funded in 2003 by the
11 Entertainment Industry Foundation and the American
12 Legacy Foundation, now called the Truth Initiative, in
13 an effort to reduce the prevalence of smoking in the
14 movies by helping everybody in the movie industry to
15 quit smoking. Over the past 15 years, we've helped
16 thousands of smokers quit using FDA-approved
17 medications and behavioral support.

18 I, like at least one member of the committee,
19 am also an ex-smoker. I come from a family of heavy
20 smokers. My father was a 4-pack-a-day smoker. That's
21 80 cigarettes per day. My mother was a 3-pack-a-day
22 smoker, and my sister and I were both 2-pack-a-day

1 smokers. Quitting smoking for me was the hardest thing
2 that I've ever done, and like many, it took me several
3 times before I quit for good, because similar to most
4 addictions, smoking can be a chronic relapsing
5 disorder.

6 During my presentation today, I will cover the
7 science of nicotine addiction and how nicotine
8 replacement works, the pharmacokinetics and
9 pharmacodynamic studies that support the development of
10 the nicotine mouth spray, and the results from the two
11 pivotal efficacy trials.

12 Let's start with the science of addiction and
13 mechanisms of NRT. Why is it so difficult to quit?
14 Tobacco dependence has three major components: the
15 physical dependence on nicotine, the use cigarettes as
16 a psychological or emotional coping strategy, and the
17 behavioral or habitual aspects in which activities are
18 situations, like drinking coffee, driving to work, or
19 taking a break, become so strongly associated with
20 smoking that they can trigger powerful cravings to
21 smoke. For many smokers, cigarettes are like their
22 best friend, always there when they need them and never

1 talking back.

2 Behavioral support helps smokers learn how to
3 deal with the psychological and behavioral aspects of
4 smoking with the goal of becoming a comfortable
5 non-smoker. That is always our goal. Behavioral
6 support can be provided through a variety of
7 modalities, written materials, face to face or
8 telephone counseling, or through tailored websites or
9 smartphone applications.

10 Nicotine replacement therapy, or NRT, has been
11 widely accepted. It's a proven treatment to help
12 manage the physiological basis of nicotine addiction,
13 allowing smokers more energy to deal with the
14 psychological and behavioral components. NRT does not
15 take away all of the craving but reduces the craving,
16 making it more manageable.

17 As a refresher, let's take a closer look at
18 the physical component. Like most drugs of abuse,
19 nicotine stimulates the release of the neurotransmitter
20 dopamine in the nucleus accumbens, the reinforcing
21 pleasure center of the brain. It only takes 10 seconds
22 for nicotine from a cigarette to be absorbed into the

1 bloodstream, pass through the blood-brain barrier, and
2 bind to the alpha 4 beta 2 acetylcholine receptors in
3 the brain, resulting in dopamine release.

4 It is this rapid release of dopamine that is
5 so reinforcing to the smoker. But the half life of
6 nicotine is only about 2 hours, and over months and
7 years, many smokers will experience moderate to severe
8 withdrawal symptoms, including strong cravings,
9 irritability, mood swings, and other withdrawal
10 symptoms, as noted on the slide, when they try to stop.

11 It is the strong craving and withdrawal that
12 leads most smokers back to smoking within a few days or
13 weeks of making a quit attempt. Each time I tried to
14 quit smoking, and that was before NRT, the first few
15 weeks were absolute torture, as every 10 seconds it
16 seemed I would have to struggle with rushing out to buy
17 a pack of cigarettes.

18 Medicinal NRT was developed to reduce craving
19 and withdrawal by stimulating the same nicotinic
20 receptors in the brain. Before nicotine gum was
21 approved in the U.S., I taught smoking classes for the
22 American Cancer Society, where the vast majority of our

1 time was spent on trying to manage these acute cravings
2 and withdrawal.

3 Shortly after nicotine gum was approved, I
4 took a position as the intervention director of the
5 UCLA site of the NIH sponsored lung health study in
6 charge of helping 300 smokers with mild to moderate
7 COPD quit and stay quit for five years. I was
8 absolutely amazed at the differences in the groups from
9 the American Cancer Society to the lung health study.
10 When they used enough nicotine gum, our conversations
11 became much less about withdrawal symptoms and strong
12 cravings, but more about how to deal with the
13 psychological and behavioral triggers to smoke. At
14 that point, I became a firm believer in the efficacy of
15 NRT.

16 OTC NRT currently comes in several formats and
17 dosages, as we heard earlier, including patches, gum,
18 and lozenges. Each form has similar efficacy, but each
19 dosage format has unique features that provide choice
20 for smokers ready to quit. Some prefer the patch
21 because it only requires a once-a-day application,
22 provides sustained release of nicotine throughout the

1 day, reducing background cravings.

2 The nicotine gum and lozenge are designed more
3 for acute craving and come in 2- and 4-milligram
4 strengths with the 4-milligram dose recommended for
5 more heavily dependent smokers. Some smokers like the
6 gum because of the chewing action, while others prefer
7 sucking on a lozenge.

8 The new nicotine mouth spray would provide an
9 additional option for smokers, providing acute craving
10 relief for the fast onset of action and flexible dosing
11 based on the urge to smoke. Also, we know that it
12 often takes multiple quit attempts before smokers quit.
13 When some smokers relapse, they often like to try a
14 different form of NRT than what they've used before.
15 So the more options that we have, the better.

16 The various products also have different
17 directions for use based on their dosage forms. The
18 gum requires a user to chew for a few seconds to
19 release the nicotine parts, a piece of nicotine between
20 the cheek and gum until the peppery taste goes away to
21 allow the nicotine to be absorbed through the oral
22 mucosa. This chew-and-park process is repeated for

1 about 30 minutes until all the nicotine in the gum is
2 released.

3 The lozenge instructions are somewhat simpler
4 in that the user only needs to move the lozenge around
5 the mouth occasionally until it dissolves over about 30
6 minutes. The mini lozenge offers the same
7 effectiveness with a shorter dissolution time. With
8 the nicotine mouth spray, the product is sprayed
9 directly into the mouth.

10 All forms of NRT involve a gradual reduction
11 of dose that takes place in three steps over a 12-week
12 treatment period. The goal is to be smoke-free and
13 nicotine-free within that time frame, but over the
14 years, we've found that many smokers may need a longer
15 treatment period to get quit or prevent relapse, and
16 therefore the labeling has been changed to allow for
17 longer term use.

18 The directions for the gum and lozenge and
19 mini lozenge involve a fixed regimen as we've heard.
20 Initial instructions are to use one piece every 1 to
21 2 hours to keep cravings to a minimum, and for strong
22 frequent cravings, to use an additional piece each hour

1 if needed. For tapering, the time between doses is
2 gradually increased.

3 In contrast, for the nicotine mouth spray, it
4 only requires 1 to 2 quick sprays into the mouth. The
5 frequency of use is flexible and based on the
6 individual's urge to smoke. In some ways this is a
7 simpler instruction than having to use it on a rigid
8 schedule and more intuitive for the smoker.

9 This more personalized approach to dosing puts
10 the smoker in control of their dosing schedule within
11 the recommended limits of 4 sprays per hour and a
12 maximum of 64 sprays per day. Tapering includes
13 reducing the number of sprays over time, and typically
14 for smokers, the number of cravings that they have is
15 reduced over time.

16 Now, let's more closely look at the rationale
17 for the development of the nicotine mouth spray. In
18 our clinical practice, we do often hear smokers tell us
19 that the gum and lozenge do not provide the more rapid
20 release of nicotine that many smokers may desire. By
21 delivering a metered dose spray in a readily absorbed
22 solution to the oral mucosa, NMS can deliver nicotine

1 to the brain more quickly and potentially provide
2 faster craving relief.

3 The NMS pharmacology program was designed to
4 investigate this. The program was quite extensive and
5 included 4 pharmacokinetic and 1 pharmacodynamic study.
6 A total of 340 subjects were included in this program.
7 An early but important PK study showed that the area in
8 the mouth where the product was sprayed did not
9 significantly affect absorption. A second study showed
10 that taking 2 sprays 20 seconds apart did not affect
11 absorption compared to taking 2 sprays at the same
12 time. The third and fourth PK studies and the
13 pharmacodynamic study, we'll discuss those more fully
14 in the next three slides.

15 Protocol 1065 was a crossover, pharmacokinetic
16 study comparing nicotine mouth spray to nicotine gum
17 and lozenge over 60 minutes after 12 hours of
18 abstinence from all nicotine. After 12 hours
19 abstinence, there's very little nicotine left in the
20 bloodstream, and most smokers have strong cravings at
21 that point.

22 Here you can see the PK curves for 4-milligram

1 lozenge and 4-milligram gum. The slope rises gradually
2 with Cmax or the peak concentration of nicotine not
3 occurring until about 30 minutes. In contrast, here
4 are the results for 1-milligram, 2-milligram, and
5 4-milligram doses of nicotine mouth spray.

6 The results clearly demonstrate that for all
7 3 dosages of NMS, the slope rises more quickly within
8 the time to maximum concentration, or Tmax, occurring
9 at about 10 minutes or less and delivers more nicotine
10 to the bloodstream during the first 10 minutes as
11 measured by the area under the curve, than the
12 4-milligram gum or lozenge.

13 However fast is relative, and as you can see,
14 the nicotine absorption from a cigarette is much faster
15 and much higher. Here we're representing the typical
16 venous plasma concentration of nicotine following a
17 single cigarette. The fast absorption of nicotine from
18 the nicotine mouth spray is enough to reduce craving
19 and withdrawal but with much less abuse liability
20 potential than a cigarette.

21 Protocol 1066 shows it with the flexibility of
22 dosing up to 4 1-milligram sprays per hour. Smokers

1 can essentially bracket the steady-state levels
2 achieved through once-per-hour dosing of the
3 4-milligram gum or lozenge over a 12-hour period. In
4 the blue and orange, you see the steady-state levels of
5 the gum and the lozenge. In red, you see the level
6 from 2 consecutive sprays once per hour of the nicotine
7 mouth spray, which is lower than for the gum or
8 lozenge.

9 In the green, you can see the highest dose,
10 which will be 2 milligrams sprayed every 30 minutes,
11 corresponding to the maximum recommended dose of
12 4 milligrams per hour, resulted in slightly higher
13 nicotine plasma concentrations compared to a
14 4-milligram lozenge or gum. With the labeling
15 flexibility of up to 4 sprays per hour, smokers have
16 the ability to titrate their usage to combat their
17 individual craving and withdrawal.

18 The next question is whether the faster
19 absorption is mirrored when looking at craving relief.
20 This pharmacodynamic study compared mean reduction and
21 urge to smoke for the 2- and 4-milligram nicotine
22 lozenge versus the 2-milligram nicotine mouth spray.

1 Two milligrams was chosen to simulate the labeling to
2 add a second dose within a few minutes if more relief
3 is desired. As you can see, 2-milligram nicotine mouth
4 spray provided significantly faster relief than both
5 the 2- and 4-milligram lozenge starting with the first
6 observation at 1 minute and continuing through
7 10 minutes.

8 Now, let's turn to the pivotal efficacy data.
9 The two types of trials in the NMS, as previously
10 described in the pivotal program, were intentionally
11 very different in design as recommended by the FDA
12 during discussions with the sponsor and consistent with
13 the recently published FDA guidance.

14 The design of the Standard efficacy trial
15 features assistance from trial staff in terms of how to
16 use the product and verbal behavioral support
17 administered at various intervals. These augment the
18 information provided through written materials and
19 reflects the clinical trial design used to support
20 previous FDA approved forms of NRT to provide evidence
21 of product efficacy.

22 The Naturalistic trial essentially eliminates

1 the intervention by trial staff, so no instructions on
2 how to use the product or any verbal behavioral
3 support. Subjects rely on the product labeling alone,
4 and we have heard in this case it's the drug facts
5 label on the carton and a user's guide insert. This
6 type of study provides evidence that consumers can use
7 the product successfully in an OTC environment without
8 the intervention of a healthcare professional.

9 As we'll discuss further, the Naturalistic
10 study conducted for NMS is significantly different in
11 several ways from previous trials to support approval
12 of NRT. The two phase 2 and 3 multicenter,
13 placebo-controlled, smoking cessation clinical trials
14 were conducted on the 1-milligram NMS.

15 The first study, we'll refer to as the
16 Standard efficacy study 11, was conducted in the EU in
17 2009 and 2010. This was a 52-week study. A total of
18 479 subjects were enrolled, 318 on active, 161
19 receiving placebo, and 242 subjects completed the full
20 study. The second study, we'll call this Naturalistic
21 study 38, was conducted in 2015-2016 in the U.S. with a
22 total of 1198 subjects, 597 active and 601 placebo,

1 again, randomized to double-blind treatment.

2 The sample size was driven by a number of
3 factors, including safety considerations, anticipated
4 dropout rates, and assumptions about quit rates. The
5 sponsor followed FDA's recommendation on quit rates
6 informed by other NRT trials and are actually higher
7 than those originally proposed by the sponsor.
8 Overall, 717 subjects completed this 26-week study.

9 Both studies shared the same primary endpoint
10 of continuous carbon monoxide verified, smoking
11 abstinence from weeks 2 to 7. A strict measure of
12 success in which a single puff of smoke from the week 2
13 visit to the week 6 visit is considered a treatment
14 failure.

15 In smoking cessation clinical trials, the
16 design variables listed on this slide can have a
17 profound impact on the study outcomes. Let's start
18 with the Standard efficacy trial. Just to review,
19 subjects were provided with verbal instructions on
20 product use, as well as written usage instructions.
21 They also received verbal behavioral support in the
22 form of face-to-face verbal counseling from trained

1 study staff at baseline in each subsequent visit. This
2 is similar to many phase 2 and 3 smoking cessation
3 studies that have been conducted.

4 In this trial, product labeling specifically
5 prohibited use of the product while smoking. This was
6 provided in the form of a do-not-use warning on the
7 drug facts label and was reinforced by the study staff
8 at each visit. Finally, subjects were directed to
9 establish their quit day as the next day, the day after
10 they started the nicotine mouth spray.

11 In comparison, the Naturalistic trial was
12 quite different in design. In this study, subjects
13 were provided with no verbal instruction on product
14 use. There was no verbal behavioral support. There
15 was no warning not to smoke while using the product,
16 which was in line with the commercial NRT label at this
17 time, which had been changed. And the user's guide
18 talked about slip ups and how to get back on track if
19 you were to smoke a cigarette.

20 Although this encouragement is useful in real
21 life, it's not entirely compatible with a clinical
22 trial setting applying a strict definition of treatment

1 failure. They were encouraged, but not directed, to
2 set the quit day for the next day, which was the day
3 that the labeling also directed them to start in the
4 study design, to start using the nicotine mouth spray.

5 The FDA briefing document calls out the Commit
6 Lozenge trial as a relevant historical comparator to
7 the Naturalistic study, however, key design elements
8 more closely resemble the Standard efficacy trial.
9 One, subjects were provided with verbal instructions on
10 product use as well as written usage instructions.

11 Two, they also received verbal behavioral
12 support with times exceeding those of the Standard
13 trial for NMS at the first four visits. Product
14 labeling included the do not warning not to smoke while
15 using the product.

16 In addition, subjects were provided with a
17 full week of preparation for their quit attempt between
18 screening and their study directed quit date, which was
19 a week later, which was not provided in either the NMS
20 standard or efficacy trials. These are all very
21 important distinctions.

22 Now that you understand the study design

1 differences between the two pivotal studies that were
2 conducted, we'll move on to a discussion of the
3 results. For the Standard efficacy trial, the 4-week
4 quit rates at week 6 -- that was no smoking from week 2
5 to week 6 -- were 26.1 percent for active and 16.1
6 percent for placebo, with a statistically significant
7 odds ratio of 1.83. As is typical in smoking cessation
8 studies, continuous abstinence rates decline somewhat
9 over time, but at 52 weeks, there was still a highly
10 significant difference between active and placebo, with
11 an odds ratio of 2.71.

12 The same approximate doubling of the quit
13 rates between active and placebo holds true for the
14 Naturalistic efficacy trial at each time point through
15 the full 26 weeks of the study. The rates for the
16 primary endpoint, not a single puff from a cigarette
17 from week 2 to week 6, were 5 percent for active and 2
18 and a half percent for placebo. The lower overall
19 rates compared to the Standard efficacy trial are
20 expected due to this naturalistic design.

21 As Dr. Hughes will discuss in more detail,
22 it's very important to start with a comparison of the

1 placebo rates as a baseline and then compare the odds
2 ratios to determine the relative efficacy when
3 attempting to make comparisons between any NRT studies
4 that may have been conducted in different eras with
5 differing levels of behavioral support or included
6 different populations.

7 This chart graphically confirms that both
8 trials with and without verbal support achieve an odds
9 ratio of approximately 2 at each time point,
10 demonstrating that NMS essentially doubles the quit
11 rate in comparison to placebo.

12 Personally, as a clinician, there's nothing
13 more gratifying than helping smokers accomplish the
14 single most important behavior change they may ever
15 make for their health and the health of others since
16 quitting smoking can also have a cascading effect
17 within the social circle of the ex-smoker.

18 My father was a role model for me. I quit
19 smoking not too long after he did. And we see this
20 over and over again in our practice, where we help
21 smokers quit, and then their friends and relatives
22 follow their lead, often using NRT to do so.

1 In our Picture Quitting program, we had a
2 supervisor who allowed everybody in the trailer on the
3 movie set to smoke because he smoked. He quit smoking
4 in our program using NRT. He immediately went back and
5 said nobody can smoke in this trailer around us
6 anymore. A number of his other people that worked with
7 them came into our program and quit smoking. There can
8 be an amazing cascading effect.

9 There's also clear evidence that children are
10 less likely to take up smoking if their parents were
11 never smokers or if their parents have quit smoking.
12 So even fairly moderate absolute quit rates can have an
13 incredible ripple effect on further reducing the
14 overall prevalence of smoking in the United States and
15 its devastating morbidity and mortality.

16 In summary, our clinical studies prove that
17 NMS is efficacious. This was demonstrated in the
18 Standard efficacy trial and in the more Naturalistic
19 trial with no support or staff intervention. The
20 results demonstrated statistical significance for the
21 primary endpoint of continuous abstinence, not smoking
22 a single cigarette from weeks 2 to 6. Both studies

1 achieved the doubling of quit rates.

2 The nicotine mouth spray is a new dosage form
3 that offers a faster rate of nicotine delivery and a
4 different approach to dosing based on the individual
5 smoker's needs. And as a clinician, I'm looking
6 forward to offering the nicotine mouth spray as an
7 additional NRT option that many smokers may find is
8 exactly what they need to become a comfortable
9 non-smoker for life. Thank you.

10 **Applicant Presentation - John Hughes**

11 DR. HUGHES: Hello, everybody. I'm John
12 Hughes. I'm a professor in the Department of
13 Psychiatry at University of Vermont. I'm board
14 certified in addiction psychiatry, and most of my
15 clinical work has been in smoking cessation. I was
16 co-founder of the Society for Research on Nicotine and
17 Tobacco and was the founder of the Association for the
18 Treatment of Tobacco Use and Dependence.

19 I've published over 400 publications on
20 nicotine and other drug dependencies and have the most
21 cited two reviews on the efficacy of over-the-counter
22 nicotine replacement therapy. I've been a consultant

1 to Congress, the FDA, the WHO, and the White House on
2 tobacco issues. In terms of disclosure, I've received
3 consulting fees from companies that develop our market
4 smoking cessation aids and our nicotine tobacco
5 products, including consulting with the tobacco
6 companies on reduced risk products.

7 I've been asked to provide some background to
8 help in interpreting the results of the NMS studies,
9 and there are four points I'd like to make today.

10 First, Dr. Nides has already described the differences
11 between the Standard and Naturalistic studies and the
12 two pivotal studies with NMS.

13 I will describe how the results of these are
14 similar to previous NRT studies conducted using these
15 different designs. I'll present also a different way
16 of looking at abstinence, called point prevalence, and
17 apply this approach to the Naturalistic study.

18 Finally, I'll discuss why even small increases in
19 quitting can produce meaningful benefit, both to the
20 individual smoker and to public health.

21 This slide shows the long-term abstinence
22 rates of the Cochrane meta-analysis of what we call

1 Standard efficacy trials of different NRT products. I
2 would draw your attention to the outcomes that I will
3 compare with the Naturalistic trials. First, look at
4 the column labeled "control." The meta analysis found
5 that the average quit rates in the group that received
6 no medication range from 6 to 14 percent across the
7 different types of NRT.

8 In comparison, the average quit rates in the
9 nicotine group range from 14 to 24 percent across NRTs.
10 But very importantly, both scientists and clinicians
11 believe that the most valid measure of efficacy is not
12 the absolute quit rate, but it's how much the treatment
13 increases the outcome in relation to the control.

14 For example, our USPHS nicotine guidelines and
15 scientific publications from the Cochrane meta-analysis
16 made conclusions on the increase, not on the absolute
17 rate. So if we look at the last column, that shows how
18 big the increase is, you'll see that in a standard
19 efficacy trial, treatments increase quit rates by a
20 factor of 1.5 to 2.5, essentially doubling the quit
21 rates.

22 This slide shows, in contrast, the results of

1 the four Naturalistic trials of NRT that I believe are
2 most similar to the GSK Naturalistic study. Again,
3 let's go to the column labeled "control" and note that
4 the quit rates in the control groups are much lower in
5 approved NRT products in a naturalistic study, and they
6 range from 1 to 6 percent; and in the nicotine group,
7 they range from 2 to 12 percent. Then again, let's
8 look at the last column, and you can see that when we
9 look, we again see this doubling of the quit rate
10 ranges from 1.2 to 3.0.

11 So even though the absolute rates of quit rate
12 are lower, the NRT still doubled the quit rate. So
13 again, one of my most important points about
14 interpreting these studies is that even though the
15 absolute rates are lower in the Naturalistic studies,
16 the pharmacological effect of nicotine, which is
17 measured by the difference, is constant; that is, a
18 doubling of the quit rate.

19 Let me see if I can put this, again, together
20 for you. I think the study methods determine a base
21 quit rate, and a treatment has a multiplicative effect
22 over that base rate, so one can manipulate that base

1 rate by changing many different things. I think the
2 low quit rates in an NMS natural trial are probably due
3 more to the study methods than to any lack of
4 pharmacological effect. I say this because a
5 pharmacological efficacy of the mouth spray is very
6 similar in both standard efficacy and naturalistic
7 trials. Finally, it's well accepted in the scientific
8 literature that one should focus not on the absolute
9 rates but on the relative increase.

10 The quit rates that I've shown you thus far
11 are based on continuous abstinence; that is no smoking
12 for several weeks or months, not even a puff. Although
13 this is an often used and valuable outcome, I think it
14 has a problem. Many smokers have a few slips after
15 they quit, but then re-establish abstinence. or have
16 trouble at the beginning and only establish abstinence
17 after several weeks.

18 In both cases, participants with slips or
19 delayed abstinence would be counted as failures. So if
20 I say to be a success, you have to be abstinent for 28
21 days, you are abstinent for 27 days. You take one puff
22 on that 28th day, and you're considered a failure. To

1 me, that's not clinically meaningful. And in fact,
2 both our USPHS nicotine guidelines and the SRNT
3 guidelines have stated that this point prevalence
4 measure is an appropriate outcome in some trials.

5 This slide shows what these point prevalence
6 rates look for in the Naturalistic NMS trial, and you
7 can see that the rates initially increase due to some
8 smokers taking a little bit longer to establish
9 abstinence. And as one would expect, the quit rate
10 using this measure is higher, and it's about 10 percent
11 after 6 months. You'll also note that we still see
12 this doubling of the quit rates over time that we
13 always see with the pharmacological effects, and that
14 it's maintained over time.

15 This slide shows the results of several
16 earlier NRT Naturalistic trials with this point
17 prevalence outcome, and you can see that they range
18 from about 6 percent to about 2 percent. So using the
19 point prevalence measure, the Naturalistic efficacy
20 study is very similar to existing approved NRTs. So if
21 you took another NRT and ran it through this same
22 protocol, you would probably find very similar results.

1 In assessing the public health impact of
2 tobacco control interventions, we often forget that
3 smoking cessation has a huge effect on smokers' health.
4 It's more important than what they eat. It's more
5 important than how much they weigh or how much
6 exercise. We forget that little changes can be
7 important.

8 For example, my reading of the literature
9 indicates that tobacco control intervention such as
10 increases in taxes, physician advice, and other items
11 usually produce increases of quitting of less than
12 10 percent. Also, the UK National Institute for Health
13 and Clinical Excellence, which advises the UK on which
14 medical costs should be reimbursed, states that small
15 increases similar to the Naturalistic trial are worth
16 funding.

17 Another way to assess public health
18 significance, as noted by the FDA, is to examine the
19 number needed to treat. The number needed to treat is
20 the number of patients that one would have to treat to
21 obtain one beneficial outcome. The FDA noted that the
22 2.5 percent increase in quit rates in the NMS

1 Naturalistic trial resulted in an NNT of 40. This 40
2 may seem large, but let me put it into context.

3 Here are the NNTs for use of many different
4 medications to prevent a heart attack, and these range
5 from 43 to 104. So even a smoking cessation NNT of 40
6 compares favorably to some important medical events.
7 Finally, in addition, I have to say that if we were to
8 rerun the study and allow people to have availability
9 of behavioral support and availability of instructions,
10 which often occur in a naturalistic study, that NNT
11 would probably be even more favorable.

12 In summary, I hope I've convinced you of four
13 things: first, that the low quit rates in the GSK
14 Naturalistic study are probably due mostly to study
15 methods, not the lack of pharmacological efficacy;
16 second, that the low quit rates in the GSK Naturalistic
17 study would be expected given what we know about prior
18 naturalistic studies of NRT, that is a doubling of the
19 quit rates; thirdly, that the NMS point prevalence data
20 is consistent with or greater than the point prevalence
21 abstinence rates of other NRTs from naturalistic
22 trials; and fourthly, that even quit rates of small

1 magnitude are worthwhile.

2 My last comment is that consideration of a
3 product must be based on comparing its risk and
4 benefits. To me, the likelihood of significant harm
5 from OTC NRT products is really small; and given the
6 devastation produced by smoking, making NMS available
7 to smokers can be substantial for both the individual
8 smoker and public health. Thank you.

9 Now, Dr. Mishra will present.

10 **Applicant Presentation - Rajesh Mishra**

11 DR. MISHRA: Thank you, Dr. Hughes.

12 Good morning. My name is Raj Mishra. I serve
13 as vice president for global medical and clinical
14 sciences at Johnson & Johnson Consumer Health. When
15 working as a clinical resident in head-neck oncology, I
16 have seen firsthand the struggle of smokers. To this
17 day, the picture of a smoker I operated on for
18 laryngeal cancer, sitting in his bed smoking through
19 his tracheostomy tube is forever imprinted in my mind.

20 I have worked in clinical research for over 20
21 years and have worked on smoking cessation projects for
22 over a decade across two companies. I'm here today to

1 review the safety profile data for nicotine mouth spray
2 or NMS.

3 In the safety section, I will cover the
4 following four topics as a foundation to the overall
5 benefit-risk considerations for the nicotine mouth
6 spray. First off, I will briefly review the extensive
7 safety experience with nicotine replacement therapy
8 since its first availability more than 40 years ago,
9 starting as a prescription medicine and then available
10 over the counter for over two decades.

11 Next, I will present the clinical safety
12 experience through the development program for the
13 mouth spray. This will be followed by reviewing
14 highlights from the cumulative postmarketing safety
15 experience with nicotine mouth spray, which is widely
16 available as a smoking cessation option in many
17 countries around the world. Lastly, I will discuss
18 some specific considerations that are relevant to the
19 safe use of the mouth spray in an OTC environment.

20 Let's begin by taking a look at the overall
21 safety experience of nicotine replacement therapy. The
22 NRT safety profile is well established through an

1 extensive body of clinical trial evidence from over 110
2 studies and more than four decades of global
3 postmarketing use, including two decades of use in the
4 OTC environment.

5 Nicotine replacement therapy is a proven safe
6 and effective smoking cessation option. If we look at
7 the global NRT exposure data for all NRT dose forms in
8 the 11-year period from 2008 to 2018, the exposure is a
9 staggering 22 billion units, one unit being one gum,
10 one lozenge, or one patch.

11 In order to better serve the needs of smokers
12 seeking to quit, the mouth spray was developed as a new
13 oral dose delivery form, receiving first marketing
14 authorization approval in 2010 and was first launched
15 in 2011. Since then, it is available as a
16 nonprescription smoking cessation medicine in 45
17 countries.

18 During the period between 2011 to 2018, the
19 exposure data for the mouth spray is 21.3 million
20 units, equating to 3 billion sprays. Together these
21 data demonstrate very wide exposure and use of all NRT
22 dose forms, including significant postmarketing

1 exposure experience with the nicotine mouth spray.

2 Now, I will review the clinical safety
3 experience for the mouth spray. First, I will briefly
4 outline the exposure experience gained with the mouth
5 spray through the course of the clinical development
6 program and illustrate the most relevant adverse
7 experience data. Next, I will highlight elements from
8 the postmarketing data that are important for the
9 overall safety profile of the mouth spray widely
10 available as a nonprescription product in many markets.

11 Through the course of the clinical development
12 program, more than 1500 people were exposed to the
13 nicotine mouth spray. This includes exposure
14 experience from phase 1 pharmacology studies, a phase 2
15 craving relief study, a usage pattern study, as well as
16 significant exposure experience from over 900 subjects
17 from the two long-term phase 3 studies. From clinical
18 trials, as well as postmarketing experience for other
19 OTC oral NRT forms such as gum and lozenge, it is well
20 recognized that the most common adverse events are
21 generally local in nature.

22 Let's first examine the adverse event

1 experience in the pharmacokinetic studies as well as
2 the craving study. Four of these studies had a
3 comparator NRT. We noted local adverse reactions to be
4 generally similar to comparator NRT, with a higher
5 frequency of a few events; for example, hiccups, throat
6 irritation, and nausea. Importantly, no deaths or
7 treatment related serious adverse events were observed.

8 Let's now take a look at the
9 treatment-emergent adverse events of all causality in
10 the context of long-term pivotal clinical trials.
11 These data are from the two completed phase 3 studies,
12 study 11 and study 38. Most frequent adverse events by
13 preferred term are those experienced by more than 5
14 percent of subjects in any treatment group. As
15 highlighted here in the red box, hiccups are by far the
16 most common, none are serious, and they go away.
17 Hiccups are included in the product label for the mouth
18 spray.

19 When we specifically examine adverse events
20 leading to subjects discontinuing in these same
21 studies, the discontinuation rate was low for the most
22 prevalent adverse events such as hiccups and throat

1 irritation, and overall was generally low in the
2 nicotine mouth spray group.

3 I will now discuss key elements from the
4 postmarketing safety experience. A comprehensive
5 cumulative review of the adverse event data for the
6 mouth spray in the period from 2011 to 2018 revealed
7 over 4,800 adverse event cases. During this reporting
8 period, approximately 21 million dispensers were sold,
9 equating to a potential exposure of approximately
10 3 billion sprays.

11 Overall, there is a low rate of adverse events
12 experience with a nicotine mouth spray. One fatal case
13 was reported, and this was not considered to be
14 treatment related. Sixteen cases were reported in
15 individuals younger than 18 years of age, and none of
16 these were serious.

17 We specifically examined the adverse events in
18 serious cases and took a closer look at the preferred
19 terms from these cases. You will note that drug
20 dependence, nicotine dependence, or dependence show up
21 several times. Dependence is coded as an adverse event
22 whenever a reporter mentions any kind of dependence to

1 the product or nicotine, or if they have used the
2 product in excess of 6 months or in large quantities.

3 The company sets a low threshold, erring on
4 the side of caution, when determining whether or not to
5 consider reporter's dependence, and we always consider
6 a serious by convention regardless of patient outcome.

7 To put the number of cases of dependence
8 reported with the mouth spray into context, we looked
9 at the percentage of cases for nicotine mouth spray,
10 lozenge, and gum that report dependence, and we do not
11 see a pattern of higher reporting frequency or
12 dependence with the mouth spray versus other oral NRTs
13 with slower pharmacokinetics. Furthermore, we have not
14 seen reporting of dependence in those who are nicotine
15 naive.

16 Based on our review, we believe these cases of
17 dependence with NRT reflect transfer dependence, which
18 may continue for a period of time as smokers try to
19 cope with cravings and long-standing nicotine
20 dependency in their journey to become smoke-free. In
21 fact, it's well recognized that some smokers may
22 benefit from the longer term use of NRT products to

1 keep them tobacco free. For these reasons, we do not
2 feel these reports of dependence with the mouth spray
3 are unexpected and do not consider them to be a safety
4 signal for NRT or the mouth spray itself.

5 Now, let's take a look at adverse events from
6 non-serious cases reported during this same cumulative
7 period. As expected, for NRT oral dose forms, the most
8 commonly reported adverse events were local in nature
9 and consistent with what was observed for the mouth
10 spray in clinical trials. These included hiccups, oral
11 discomfort, throat irritation, and nausea.

12 I'll now shift gears and discuss some specific
13 topics that are relevant to the safe use of the mouth
14 spray in an OTC environment. Review of clinical trial
15 and postmarketing safety data reveal some adverse
16 reactions that are related to the systemic effects of
17 nicotine and are generally observed with all forms of
18 NRT; for example, nausea, vomiting, headache, and
19 palpitations.

20 It is noteworthy that certain commonly
21 reported adverse events are associated with smoking
22 cessation itself resulting from withdrawal and nicotine

1 cravings. These include emotional or cognitive effects
2 such as dysphoria, depressed mood, irritability, anger,
3 and more.

4 Importantly, differences in local reactions
5 are expected based on formulation and route of
6 administration differences. For example, nicotine gum
7 users' experience some jaw tightness and pain in the
8 jaw. Likewise, oral spray users' experience a high
9 frequency of hiccups and mouth and throat irritation,
10 which are also common adverse events across all oral
11 NRT dose forms.

12 Before I address the potential for abuse of
13 the mouth spray, I would like to take a moment to
14 clarify how abuse is defined for the purpose of NRT
15 safety reporting and the safety review. When we
16 receive an adverse event report, we capture it as abuse
17 in our safety database if one of the following applies:
18 the reporter explicitly states they are abusing NRT;
19 they describe the repeated use for a non-therapeutic
20 purpose, whether or not this use results in harm, or if
21 they're using the product to produce a euphoric effect.

22 In our aggregate safety review, we carefully

1 identified all cases of abuse by first searching our
2 database for any cases reporting an event term of drug
3 abuse, substance abuse, or one potentially associated
4 with abuse such as intentional product misuse or
5 overdose.

6 Any cases reporting terms such as intentional
7 misuse and overdose underwent a narrative level review
8 to determine if the product was used for a
9 non-therapeutic purpose with a perceived reward or
10 getting high. If yes, these were considered to be
11 abuse cases even if it was only a single use or a
12 sporadic use of the product. We believe this is very
13 similar to the strategy followed by the FDA.

14 As Sue James mentioned, the potential for
15 abuse with NRT is not a new topic. The issue of the
16 potential of these products to increase abuse,
17 particularly in an adolescent population, was totally
18 assessed at the time of the OTC approval of nicotine
19 patch, gum, and lozenge. The comprehensive program
20 undertaken at that time monitored for abuse or misuse,
21 including multiple modalities, eventually showing
22 virtually no adolescent abuse or misuse of NRT

1 products.

2 No signals of abuse have been seen with
3 existing forms of OTC NRT in postmarketing reporting as
4 reinforced by a 2010 FDA review of historical reports
5 from 1984 to 2009, which concluded that NRT products
6 have a low potential for abuse.

7 From our cumulative review, there are very few
8 and limited reports of abuse with the mouth spray. No
9 cases reported the term "abuse" or "substance abuse,"
10 and a narrative review of all those cases did not
11 reveal any cases suggesting abuse. Review of
12 intentional product misuse case narratives identified
13 two cases that suggested the potential of abuse,
14 indicating that the product was not used to treat
15 craving but rather used to get a head rush and to get
16 high.

17 This represents a very small number of cases
18 coded with the preferred term of intentional product
19 misuse, 21 cases in total. One of these 21 cases was
20 serious, reporting a pharmacy staff member who was
21 attempting to see what the product was like and
22 experienced an asthma attack. We also looked for any

1 obvious pattern of higher frequency of intentional
2 misuse in general sales versus behind-the-counter
3 markets and did not see one.

4 In summary, we have not seen a pattern of
5 abuse following the prior OTC approval of oral NRTs,
6 and similarly have not seen a pattern of abuse
7 reporting in the postmarketing data for the nicotine
8 mouth spray. We believe this supports the low
9 potential for abuse with the nicotine mouth spray.

10 Child-resistance feature is a very important
11 consideration for the safe use of this product in an
12 OTC environment. Child-resistance testing was
13 conducted with the device for standard protocols
14 required in the U.S., and the results were acceptable.

15 With regard to accidental exposure in
16 children, only two reports of non-serious cases of
17 accidental exposure to the eye have been reported.
18 Furthermore, there were no reports of administration in
19 infants or small children under 6 years of age and no
20 evidence for threat or risk of poisoning in young
21 children, underscoring that the child-resistant
22 features of this product are robust.

1 In summary, the safety profile of nicotine
2 mouth spray is consistent with other forms of OTC NRT.
3 Local adverse events with the mouth spray are similar
4 to other oral delivered NRT forms such as lozenge and
5 gum, except for a higher frequency of a few events such
6 as hiccups, throat irritation, and nausea.

7 Hiccups and mouth and throat irritation are
8 the most common adverse events, especially during the
9 first few weeks of use, and tend to decline and resolve
10 as experience is gained with product use and tolerance.
11 Based on ex-U.S. postmarketing experience, there is no
12 evidence of abuse with the nicotine mouth spray.

13 We believe the significant body of evidence
14 coming from clinical trial data and extensive
15 postmarketing experience outside the U.S. supports the
16 positive benefit-risk profile for the nicotine mouth
17 spray as an important new OTC option for U.S. smokers.
18 Thank you. I'll now invite Julie Aker to the podium.

19 **Applicant Presentation - Julie Aker**

20 MS. AKER: Thank you, Dr. Mishra.

21 Good morning. I'm Julie Aker, and I'm
22 president and CEO at Concentric Research. Concentrics

1 is a leader in conducting consumer behavior studies and
2 over-the-counter products. In the past 30 years, we've
3 conducted over 1500 studies that have supported the
4 approval of new over-the-counter drugs and devices.
5 This morning, I'm going to highlight the consumer
6 studies that were conducted for this program.

7 Over-the-counter NRT products, as you know,
8 have been available for two over two decades, and as a
9 result, it's established that consumers know how to
10 self-treat with these products. There's an established
11 and FDA-approved labeling for OTC NRT products. The
12 Nicorette Mouth Spray, or NMS, is comprised mostly of
13 information from the established NRT labeling that
14 consumers have seen for years. Therefore, we focus the
15 consumer behavior studies primarily on information
16 unique to the NMS product.

17 The NMS product have several forms of
18 labeling. There's a drug facts label on the outer
19 panel that's comprised as per FDA regulations of the
20 indication, the warnings, and the inner panel contains
21 directions from the drug facts label on the left and a
22 new quick start guide on the right, which has pictures

1 and instructions on how to use the product. And
2 there's a user guide that outlines how the product
3 works, repeats the 3-step plan, and outlines planning
4 for success, the behavioral support program also called
5 MyQuit, and managing for success.

6 Consumer research has been conducted
7 throughout the program. Prior to initiation of the
8 clinical studies, comprehension pilot studies were
9 conducted, and this was in the time frame prior to the
10 FDA label comprehension guidance being issued. After
11 the clinical studies were completed, GSK considered
12 further refinements to the labeling based on best
13 practices in label construction and on methods outlined
14 in the final FDA label comprehension guidance.

15 Two types of studies were conducted in
16 iterative testing, starting with small studies and
17 progressing to larger studies as the labeling became
18 more optimized. There were label comprehension studies
19 and human factors studies. You can see that multiple
20 rounds of testing were completed.

21 We'll begin by looking at the label
22 comprehension study. A human factors study was also

1 conducted, however, the results were very good. And
2 for the priming step, which scored slightly lower. FDA
3 agreed with our conclusion that consumers will become
4 more experienced with the use of the device over time.
5 Therefore, in the interest of time, I will focus on the
6 label comprehension study. Further information is in
7 your briefing document.

8 Label comprehension studies are conducted to
9 evaluate if the labeling is clear even to individuals
10 of limited literacy. FDA created a guidance entitled
11 "Label Comprehension Studies for Nonprescription Drug
12 Products" in 2010. The guidance outlines best
13 practices and methods and key principles for conducting
14 these studies. This program was designed based on this
15 guidance. The studies are interview only. There is no
16 drug administered.

17 The data are collected from participants in
18 one-on-one interviews after they've had an opportunity
19 to review the labeling independently and at their own
20 pace. A trained interviewer asks questions that are
21 posed in third-party scenarios. These scenario
22 questions are not about the participant personally, but

1 about a person in a hypothetical situation.

2 Here's an example. Sandy has been using this
3 product for 9 weeks. In step 1, she was using
4 10 sprays per day. The question the participant needs
5 to answer is according to the label, how many sprays
6 per day should Sandy be using by the end of week 9?

7 So the participant has to locate or navigate
8 to the information on the labeling, and then interpret
9 the label information in their response. This testing
10 is done in iterative rounds, and the table is adjusted
11 to optimize it over time prior to conducting a
12 quantitative, statistically powered, pivotal study.

13 The drug facts label provides the foundation
14 for any OTC product labeling. There's an established
15 format and content for each section of the DFL. The
16 DFL communicates information about the indication, the
17 warnings, and the directions. The format is codified
18 in the Code of Federal Regulations.

19 The content of NRT products is well
20 established, so GSK focused on the information that was
21 unique to the product for our testing. The unique
22 information was comprised of the potential side effects

1 and about the directions related to dosing, dosing,
2 frequency, and intended administration. All other
3 information on this label is in the established NRT
4 product label.

5 The pivotal study was conducted in a robust
6 sample of over 500 subjects comprised of smokers 18 and
7 older. Twenty-six percent of the population was of
8 limited literacy based on the Rapid Estimate of Adult
9 Literacy in Medicine, or the REALM test, which is a
10 validated tool to screen for health literacy.

11 Participants provided two responses per
12 question, an initial response to the question and a
13 follow-up response to explain their rationale for the
14 response. The initial response and follow-up response
15 are coded together to determine if the response is
16 correct, acceptable, or incorrect. In short, the
17 participant had to give the right answer, but for the
18 right reason in order to be scored correct.

19 A priori thresholds were established for the
20 primary endpoints. There were 4 primary endpoints and
21 8 secondary endpoints for the comprehension testing. A
22 total of 18 questions were asked. The 4 primary

1 endpoints were the maximum number of sprays per hour,
2 not to inhale while spraying, the maximum number of
3 sprays per day, and to rinse immediately with water is
4 sprayed in the eyes. A lower bound threshold of 80
5 percent was established a priori.

6 As you can see, the 80 percent threshold was
7 exceeded for 3 of the 4 endpoints and nearly met for
8 the fourth endpoint. Question 17 was the objective to
9 rinse immediately with water if you spray in the eyes,
10 as irritation will occur. It scored slightly lower
11 with a lower bound at 74 percent.

12 Of the 112 incorrect responses, 66 responders
13 did not notice the instruction on the label, but the
14 remaining 46 individuals gave us a more conservative
15 response to contact a health care provider or they
16 simply stated that the product was not intended for use
17 in the eyes.

18 While these 46 responses are technically
19 incorrect because they did not contain the exact words
20 on the label, the actions and responses indicated
21 reasonable and safe courses of action. If we would
22 have included those 46 responses in the correct scores,

1 this objective would have scored 87 percent correct.

2 There were 8 secondary endpoints, and of
3 these, 7 of the 8 exceeded the 80 percent correct
4 comprehension. These comprehension objectives were
5 also about the directions. The one lower scoring
6 objective, question 10, was related to step 3 dosing.
7 Individuals who gave incorrect responses either gave a
8 more conservative response, meaning to ask a healthcare
9 professional before use, or they referenced a different
10 part of the labeling.

11 Despite the lower scores for this subjective,
12 it is clear that participants understood the concept of
13 reducing the number of sprays over time, particularly
14 clearly understood that this is a 12-week treatment
15 program. They understood the concept in step 1 of
16 initially administering 1 to 2 sprays when they usually
17 have a cigarette or a craving, and they understood to
18 use a second spray if the cravings were not reduced in
19 a few moments. They understood that for step 2 that
20 they should start reducing the number of sprays per day
21 and that by the end of step 2, they should be using
22 half the average number of sprays that they used in

1 step 1.

2 So in summary, consumers demonstrated
3 comprehension of the unique messages in the drug facts
4 label with the primary endpoints being met or nearly
5 met. Consumers also demonstrated that they could use
6 the device under first-time use conditions with no
7 training or coaching with the Quick Start Guide by
8 locking/unlocking, aiming and spraying, and locking.
9 Priming, as with all OTC devices, is a self-evident
10 process that becomes familiar with the user over time.

11 Finally, consumers comprehended key behavioral
12 support messages in the user guide related to the
13 importance of completing the 12-week program and
14 getting prepared to quit. Now, I'd like to turn it
15 over to Sue James to conclude.

16 **Applicant Presentation - Sue James**

17 MS. JAMES: Thank you, Julie.

18 So in summary, we believe that the benefits an
19 individual experience using NMS to help them quit
20 smoking outweigh any risks associated with product use
21 and far exceed the risks of continued smoking. NMS is
22 an innovative, novel NRT dose form that features faster

1 nicotine absorption than other NRT products and
2 flexible dosing based on the individual's urge to
3 smoke, thereby putting the smoker at the heart of their
4 own dosing decisions.

5 In today's landscape, the launch of a new OTC
6 drug could draw positive attention and create renewed
7 interest in quitting, and as a drug, this product is
8 subject to rigorous standards of safety, efficacy, and
9 quality both in the pre- and post-approval settings.

10 The efficacy data from the two well-controlled
11 clinical trials establishes the benefit of the product,
12 showing clearly that the use of NMS doubles the quit
13 rate versus placebo. With these two efficacy studies
14 and the supportive craving relief study, we believe our
15 data demonstrates substantial evidence of efficacy and
16 support proposed label claims, which are shown in this
17 excerpt from the drug facts label.

18 To support the smoker in their quit attempt,
19 we've developed clear, colorful, engaging self-help
20 materials to accompany the product. We've also built a
21 suite of digital tools so smokers are surrounded with
22 the support they need to achieve and maintain their

1 quit. The website provides helpful advice, tips,
2 inspirational messages, and demonstration videos. A
3 mobile app helps users create a plan, log cigarette
4 cravings, and track personal progress. An email
5 delivers daily encouragement to their inbox that's
6 customized wherever they are in their quit.

7 This holistic support package is intended to
8 help the smoker on their quit journey, knowing that in
9 reality it may take many attempts before they can quit
10 for good. Every quit attempt matters. FDA and NIH's
11 Every Try Counts public health campaign provides
12 education and motivational messages. Smokers are
13 encouraged to practice quitting, and failure is
14 reframed as a learning experience with inspiration to
15 keep trying. If smokers do not try to quit, they will
16 not succeed, and based on ex-U.S. data, nicotine mouth
17 spray may encourage more to try.

18 NMS has a similar safety profile to other NRT
19 products established over two decades with NRT gum and
20 lozenges. J&J's postmarketing data as a nonprescription
21 product in 45 countries affirms the favorable safety
22 profile with no new safety concerns observed and low

1 abuse/misuse potential by adults and adolescents.
2 These data are consistent with GSK consumer health
3 care's extensive postmarketing surveillance of other
4 NRT formats, which demonstrated low abuse/misuse of NRT
5 under OTC conditions.

6 Like other NRT quit smoking products, NMS will
7 be promoted to adult smokers only with age verification
8 at point of purchase. Our internal pharmacovigilance
9 procedures will be followed, and consistent with
10 regulatory requirements, quarterly periodic safety
11 reports will be submitted to the FDA.

12 Overall, as with other NRT products, the
13 potential risks associated with product use are far
14 less than the risk of continued smoking. Although
15 we've made progress with reducing the rates of
16 cigarette smoking in the U.S., approximately 14 percent
17 of the adult population continues to smoke today,
18 posing significant risk of their own health and the
19 health of others by second- and third-hand smoke.

20 Cigarette smoking causes nearly half a million
21 deaths each year. Smoking causes 90 percent of all
22 lung cancer deaths and 80 percent of all deaths from

1 COPD. Smoking increases risks of coronary heart
2 disease 2 to 4 times and the risk of developing lung
3 cancer by 25 times.

4 The health benefits of quitting smoking are
5 undeniable and substantial. Over time, there's a
6 significant reduction in cardiovascular risk, stroke
7 risk drops to that of a nonsmoker, and some cancer
8 risks are halved, and within 10 years, so is the risk
9 of dying from lung cancer. The benefits of an
10 individual's quit may have a positive ripple effect on
11 others within this sphere of influence.

12 NMS represents a new NRT innovation and
13 directly addresses the 2017 call to action from FDA
14 that encourages research of innovative NRT therapies.
15 The former FDA commissioner, Dr. Scott Gottlieb, made
16 statements in 2018 about FDA's commitment to smoking
17 cessation, recognizing the importance for our nation's
18 health of significantly reducing the rate of
19 tobacco-related disease and death. He stated that the
20 development of novel NRT products regulated as new
21 drugs is a critical part of our overall strategy on
22 nicotine, and that the use of FDA-approved NRT products

1 is generally considered to double the likelihood of a
2 successful quit attempt, which we have shown NMS does.

3 GSK has been committed to smoking cessation
4 products for over 20 years in the marketing of gum,
5 lozenge, patch, and now with our application for the
6 NMS spray. We believe that this product rises to the
7 challenge that FDA has put forth for innovation with
8 associated public health benefit as another choice to
9 help smokers reduce withdrawal symptoms.

10 Overall, the NMS development program was
11 comprehensive and aligned to the current FDA guidance.
12 NMS doubles the rates of quitting. It has a well known
13 and favorable safety profile and significant
14 postmarketing experience as a nonprescription medicine,
15 and it challenges FDA's call to industry to step up and
16 provide new options.

17 We believe the data presented today provide
18 substantial evidence of safety and efficacy for the OTC
19 use of nicotine mouth spray, and that it is important
20 to act to make this product, currently available to so
21 many smokers worldwide, an option for the U.S. smoker
22 trying to quit.

1 I thank the committee and FDA for their kind
2 attention. This concludes the sponsor's core
3 presentation. We're now ready to answer your
4 questions, and I would like to reintroduce Dr. Raj
5 Mishra from our business partner, J&J, as our
6 moderator.

7 **Clarifying Questions**

8 DR. NEILL: Thank you, and thank you for
9 getting us ahead of time.

10 Are there any clarifying questions for GSK
11 from the committee? If you have some, please remember
12 to state your name for the record before you speak, and
13 if you can, please direct your question to a specific
14 presenter. If you have a question, hold your hand
15 until you've gotten the attention of Dr. Chee or
16 myself.

17 Abigail, let's begin with you. Others, please
18 keep your hand up until we've gotten your attention.

19 DR. SHOBN: Sure. This is Abby Shoben. My
20 question is about recruitment, particularly for that
21 naturalized clinical trial that took place in the U.S.
22 How are you recruiting individuals who are willing to

1 sort of take part in this experiment, where they were
2 going to get very little, except for, I assume, a 50/50
3 chance a free NRT?

4 DR. MISHRA: I'd like to invite Dr. Mitch
5 Nides to address that question, please.

6 DR. NIDES: Mitchell Nides, Los Angeles
7 clinical trials. Recruitment for this study, as you
8 can see in the Naturalistic study, over I think it was
9 8 to 10 sites. I'm not sure exactly how many, but
10 about 8 sites across the country and across different
11 regions. We recruited approximately 1200 subjects.
12 I've been recruiting for these types of studies since
13 1993 I believe, so for quite a while.

14 The way that we recruited was
15 through -- slide 1 up -- through advertisements. There
16 was typical television spots. There was marketing
17 through social media as well, through Facebook, through
18 Google. The outreach, it's amazing how many people
19 still want to participate who are smokers and really
20 want to try to quit smoking.

21 When they see an ad that says there's
22 something that might work for them, they're still

1 excited about participating, even if they know that
2 they're going to have a 50 percent chance of getting a
3 placebo and not getting as much behavioral support as
4 they might in something else. It's just amazing how
5 many people still want to quit smoking.

6 You can see here what we were using. The
7 techniques that we were using to recruit for this were
8 very similar to what we've used over the years. You
9 find different populations over the years that come
10 into these trials. When you look at some of the
11 demographics, it more closely mirrors the demographics
12 of smokers today than mirrored the demographics of
13 smokers for other phase 2 and phase 3 trials.

14 DR. NEILL: I have Dr. Curry, then Dr. Farber,
15 then Dr. Parker. Dr. Curry?

16 DR. CURRY: I have two quick questions,
17 clarifying questions, about the human factors study.

18 DR. MISHRA: Can I invite Julie Aker, please?
19 Thank you.

20 DR. CURRY: The first one -- and I may have
21 missed this -- is this was an N of 39 study. I'm
22 interested in whether smokers who used e-cigarettes

1 were eligible.

2 MS. AKER: Do we have the inclusion/exclusion
3 for the human factors? This was a group of smokers 18
4 to 54. We don't have a slide that tells whether -- I
5 can pull that up for you at the break, though.

6 DR. CURRY: Then I just wanted to clarify that
7 any potential inhalation of the mist was purely based
8 on an observer behind a one-way mirror looking at the
9 person using it. Is that correct?

10 MS. AKER: That is one way. We also
11 videotaped it because we wanted to be sure -- so there
12 was a camera in the room, even though there wasn't a
13 person in the room, so we videotaped each and every one
14 in the event that the observer didn't see something
15 that was subtle, and we reviewed those at the end.

16 DR. CURRY: Thank you.

17 DR. NEILL: Dr. Farber?

18 DR. FARBER: So I also have two quick
19 questions.

20 DR. NEILL: And if you could remember, for
21 committee members, even though I'm addressing you by
22 name, for our important transcriber, please list your

1 name before your question. Thanks.

2 DR. FARBER: Neil Farber. I have two quick
3 questions; one for pharmacokinetics. On slide 31, at
4 the tail end of those graphs, it appears that there is
5 an increase in craving for the nicotine mouth spray
6 above the others, and I'm wondering if that's
7 significant.

8 The other question is for the safety issue.
9 Regarding misuse, I noticed you didn't address the
10 issue of patients who continued smoking despite using
11 the nicotine mouth spray. I wonder if you would
12 address that.

13 DR. MISHRA: Thank you. I'd like to invite
14 Dr. Nides to address the first part of the question.

15 DR. NIDES: Mitchell Nides, Los Angeles
16 clinical trials. As you can see from slide 31, the
17 only significant differences that there were in
18 reduction in craving were between the NMS and the
19 others through the first 10 minutes. So there was no
20 significant differences among the products going out to
21 120 minutes.

22 DR. MISHRA: I just want to clarify your

1 second question. This is regarding misuse from the
2 safety postmarketing. Could you please rephrase that?

3 DR. FARBER: Yes. For the safety issue, you
4 talked about intentional misuse. There was an
5 approximate three-quarters of the subjects who
6 continued smoking despite using the nicotine mouth
7 spray compared with about a quarter when patients were
8 using -- in other studies when patients were using
9 lozenges. And I wonder if somebody would address that.

10 DR. MISHRA: Okay. This is from the clinical
11 trials, yes. So again, I'd like to invite Dr. Nides to
12 kind of put that into context in terms of ongoing use
13 of the product along with smoking from the clinical
14 trials. Thank you.

15 DR. NIDES: Mitchell Nides, Los Angeles
16 clinical trials. We did not see any additional adverse
17 events from people who were using smoking and using the
18 product at the same time. Typically, what you see in
19 these trials is even those that are using it at the
20 same time have reduced their cigarettes per day. In
21 this study, you saw using about half the cigarettes per
22 day. So over all trials, over all time, we have not

1 seen a significant increase in adverse events.

2 If you're comparing the number of people in
3 the NMS study that we're continuing to use, first, the
4 lozenge study, for example, one of the key differences
5 in the design of the NMS versus the lozenge study was
6 that in the lozenge study, starting with week 2, which
7 was the start of the efficacy period, if they came to
8 the week 2 visit and said that they had smoked a single
9 puff off of a cigarette, they were dismissed from the
10 study.

11 So at each additional visit, anybody who had
12 smoked and could not meet the efficacy criteria was
13 dropped from the study. So you see much less dual use
14 during the study. If you go back to earlier studies
15 and look at patch studies and gum studies that allow
16 people to use the product over the full course, you are
17 going to see quite a bit of dual use during the course
18 of the study.

19 DR. MISHRA: Does it address your question?
20 Hopefully. Thank you.

21 DR. NEILL: I have Dr. Parker, then
22 Dr. Zorich, Curry, and Krishnan-David [sic].

1 DR. PARKER: Ruth Parker. I have three
2 specific questions to label comprehension. If you
3 could pull up the slide CC, I think it's 81, that was
4 presented. I want to make sure I understood correctly.
5 The content for label comprehension studies focused on
6 what's in the red, what's highlighted in the red here.

7 Did I hear that correctly?

8 DR. MISHRA: I'll invite Julie Aker to address
9 your questions one by one. Thank you.

10 MS. AKER: So there's a lot of red on that
11 slide, so let me clarify. The carets on the outside
12 are just really speaking to the parts of the label, so
13 the interior boxes are the ones that we're talking
14 about, yes.

15 DR. PARKER: Okay.

16 MS. AKER: On the left, it would be the when
17 using and on the right, it would be the direction
18 section.

19 DR. PARKER: So specific to that, there were
20 no label comprehension questions that allowed you to
21 know whether or not people knew that this was a
22 nicotine product, that the active ingredient is

1 nicotine. That was not felt to be an essential part of
2 label comprehension?

3 MS. AKER: We did ask the question -- can you
4 pull up the --

5 DR. PARKER: But that was not considered one
6 of the primary endpoints?

7 MS. AKER: It was actually asked in the user
8 guide questions that we asked in the human factor
9 study. So we did test it in that group.

10 DR. PARKER: But that's in a small N.

11 MS. AKER: That's true.

12 DR. PARKER: Okay.

13 MS. AKER: That's true. This is an
14 established label, so, yes, we did not test the purpose
15 statement because that's considered to be something
16 that's established for all NRTs.

17 DR. PARKER: Okay. I just want to make sure I
18 was clear on that. So you do not have beyond the human
19 factor small N input on how many people from label
20 comprehension knew that this was a nicotine.

21 MS. AKER: We did not test that since it's
22 established, no.

1 DR. PARKER: Got it. I understand there were
2 18 questions; 4 of them were primary endpoints, and
3 among none of the endpoints was whether or not it was a
4 nicotine product. There were 8 that was secondary. I
5 had a specific question to the primary endpoint
6 question about inhaling. How was that question asked?

7 MS. AKER: I don't know if we have the
8 question from the questionnaire on that one.

9 DR. PARKER: If you could get that --

10 MS. AKER: I can get that one for you.

11 DR. PARKER: -- and show it after break, that
12 would be great --

13 MS. AKER: Certainly. I'd be happy to.

14 DR. PARKER: -- exactly how that was asked,
15 because I know that came up in terms of the human
16 factors and how it was demonstrated.

17 MS. AKER: Sure.

18 DR. PARKER: And I'm just thinking about what
19 we know about the public's ability to understand that
20 word and how it's demonstrated.

21 MS. AKER: Certainly.

22 DR. PARKER: So if you could show us how it

1 was asked and how it was answered.

2 MS. AKER: Certainly.

3 DR. PARKER: Then I was curious if you could
4 also provide the answers to the six other label
5 comprehension study questions that weren't included.

6 MS. AKER: Sure.

7 DR. PARKER: That would be great.

8 MS. AKER: Yes, absolutely.

9 DR. PARKER: And I understand you decided not
10 to use those primary or secondary outcomes.

11 The other question I had was what's the font
12 size of all the package labeling on the final product?

13 MS. AKER: We actually do the testing in the
14 actual product, so it wasn't larger, if that's your
15 underlying question.

16 DR. PARKER: What is it, the size?

17 MS. AKER: I'll have to look to see what the
18 actual size --

19 DR. PARKER: If you will give us that number
20 when you --

21 MS. AKER: Yes, certainly.

22 DR. PARKER: And the other thing, if you could

1 provide a sample of the product itself --

2 MS. AKER:

3 DR. PARKER: -- its packaged labeling as it's
4 intended, and also the user guide for us to look at and
5 actually hold, that would be great.

6 MS. AKER: Sure. I'd be happy to.

7 DR. PARKER: Thank you.

8 DR. NEILL: Dr. Zorich?

9 DR. ZORICH: Thank you. Nora Zorich. I
10 wanted to make sure that I'm completely clear on the
11 evolution of various materials because the agency
12 referred to study 38 as a real-world study. The
13 sponsor refers to it as a naturalistic study. I think
14 both of those terms may communicate something
15 different.

16 But what I wanted to be clear on, if we look
17 at the sponsor's slide CC-76, all of this material,
18 this user guide -- I want to make sure I'm
19 clear -- this was not part of study 38.

20 DR. MISHRA: Let me invite Julie Aker to
21 explain the evolution of the materials, what was used
22 in study 38 and subsequently developed.

1 DR. ZORICH: And the reason I ask that is that
2 an earlier slide from Sue James, CC-4, said the MyQuit
3 was developed in 2017, so that's obviously after the
4 conduct of this study. So clearly, not all of this
5 could have been used.

6 DR. MISHRA: That's correct, yes.

7 Julie?

8 MS. AKER: Julie Aker, Concentrics Research.
9 The materials that were available for the 38 study, you
10 are correct. They were lesser than the materials that
11 were available later. So in the original -- we do have
12 quick examples here. In the original 38 study, there
13 was a drug facts label that was available, and then
14 there was also an original user guide. Afterwards,
15 there was a quick start guide that was actually
16 developed.

17 Slide 3 up. This was the original drug facts
18 label. I'm sorry for the clarity's; it's not very
19 sharp. Then slide 2 up. This is what the user guide
20 looked like, and it had 4 pages to it. It was very
21 dense; you can see. Then for the newer labeling that
22 was used, you saw a snap earlier, or a picture

1 earlier -- slide 3 up -- of the exterior. It opens
2 like a book.

3 So on the exterior, all of the indication and
4 all of the warnings are on the exterior. When you open
5 it up, it's all directions for use. So directions for
6 use on the left from the drug facts label, and on the
7 right, the new quick start guide, that quick start
8 guide was not in the original 38. It was an innovation
9 after the study as a result of the study. Those
10 pictures in a much cruder form were in the original
11 user guide.

12 DR. ZORICH: So if we go back to CC-76 again,
13 I would say that we should not refer to -- at least, I
14 don't know if we should call it naturalistic, or real
15 world, or anything like that unless we have a clear
16 understanding that if this product were approved, the
17 real-world use would include all of this.

18 MS. AKER: Yes. And I would just add that all
19 of this, when you talk about MyQuit -- and there are
20 others here that can speak about this much more than
21 I -- that MyQuit also has many digital and social
22 forums as well.

1 DR. ZORICH: Okay. Thank you for the
2 clarification.

3 DR. NEILL: So in the interest of process and
4 because we're going to be taking a break in just a few
5 moments, I still have Dr. Curry, Dr. Krishan-Sarin, and
6 Dr. Hatsukami.

7 Dr. Curry, because you've already asked your
8 question, I'm going to beg your indulgence to delay
9 until perhaps this afternoon, and we're going to move
10 on to Dr. Krishnan-Sarin. In addition, there's been at
11 least one question from Dr. Parker -- thank you,
12 Dr. Parker -- that's going to require some data from
13 GSK, and I would suggest that we may not have time
14 before our break to bring that back. So if you could
15 serve as our collective memory, we'll do that I suspect
16 later in the afternoon when we've got time for
17 questions.

18 Dr. Krishnan-Sarin?

19 DR. KRISHNAN-SARIN: Thank you. Suchitra
20 Krishnan-Sarin from Yale. I have two questions,
21 specifically related to one of the big issues that
22 we're supposed to consider, which is abuse liability.

1 In this regard, my first question, which I hope will be
2 a simpler one, relates to the inhalation issue, which
3 has already been brought up by other individuals.

4 Was there any data collected at any point
5 about what exactly is absorbed if people inhale it?
6 There is information provided stating that the
7 particles are not small enough to really go deep down
8 into the lungs and to be deposited. But my question is
9 do we actually have any evidence suggesting that if
10 somebody mistakenly inhales it, that there aren't going
11 to be any adverse consequences because the mist is
12 going to go deep into the lungs, and there is going to
13 be absorption or other adverse events?

14 DR. MISHRA: Yes. So let me clarify that.
15 The way the product was designed as we know, this is
16 meant to be a mouth spray absorbed oromucosally. So if
17 someone attempts to misuse it by trying to inhale it,
18 what's going to happen is that as they attempt to do
19 that, this will get to the back of the throat and
20 oropharynx, and result in severe kind of throat
21 irritation and the hiccups. Also, with rapid
22 absorption, they'll start feeling nauseous, vomiting.

1 So there will be a very adverse reaction. And
2 as you already pointed out, because of particle size or
3 the droplet size and such, it's not actually designed
4 or amenable to go down into the lungs. So in an
5 attempt to get it down the lungs, these things will
6 happen, and immediately be self-limiting. And we know
7 from those two reports where there were two subjects
8 who attempted to abuse this, they ended up getting kind
9 of these reactions, and that was self-limiting.

10 So as such, we feel very reassured.
11 Obviously, we haven't done any specific studies to try
12 to see what could happen and how much goes in the
13 lungs, but the reality is this is what happens if
14 someone attempts to try to inhale this product.

15 DR. ZORICH: So you have not done studies
16 about what gets in the throat.

17 DR. MISHRA: Yes, because the product is
18 not -- it would not go down into the lungs unless you
19 try to really put it at the back of the throat and
20 tried to see if this ever went down. But it's not
21 intended to go down based on the way the droplet size
22 of the product is.

1 DR. ZORICH: Okay. Then my second question is
2 about the abuse liability issues, especially related to
3 the issue of using it. Is most of the evidence you're
4 providing based on adverse events reported from use in
5 other countries?

6 DR. MISHRA: Yes. The product is not marketed
7 yet in the U.S., but we have marketed it extensively in
8 many countries outside the U.S. And as Sue James
9 pointed out, of the 45 markets, 25 are what is
10 considered self-selection, so the OTC environment is
11 very similar to the U.S. where the product can be
12 purchased the off the shelf.

13 So given the cumulative experience, we are
14 reassured that this has really not been an issue in
15 terms of adolescent abuse liability. I mean, as I
16 said, except for those two cases where adolescents
17 attempted to abuse it, and then they didn't really get
18 what they were seeking in terms of the euphoric effects
19 but ended up having a side effect, overall the
20 postmarket experience outside the U.S. is very
21 reassuring.

22 DR. ZORICH: Do you not have data from the UK

1 that you can show us on how adolescents are actually
2 using this product? Because you have been marketing it
3 there and in Canada for quite a while. Is there no
4 evidence on this that you have?

5 DR. MISHRA: We have not seen any kind of
6 abuse liability issues in those markets. And I think,
7 as Sue also pointed out, the label actually goes down
8 to 12 years of age. The product could be available for
9 younger people to use for quitting if they were
10 addicted to smoking.

11 Retailers provide their own kind of controls
12 in place before this is actually given to adolescents,
13 but under a physician's supervision or if someone
14 provided it to their adolescent child to quit smoking,
15 the product could be made available. But we haven't
16 seen any reports of adolescent abuse in those markets,
17 including UK where it goes down to 12 years of age in
18 terms of approval for marketing.

19 DR. ZORICH: Just one more point, I'm just
20 going to say that I think I'm looking forward to seeing
21 the device as well because one of the issues is, is it
22 tamper-proof, and as we've seen with U.S. youth, can it

1 be hacked, and can you do things with it, which might
2 increase its abuse liability.

3 DR. MISHRA: Yes, and we're happy to share
4 that during the lunch break. Thank you.

5 DR. NEILL: On that note, I will note that we
6 are now back behind schedule. Dr. Hatsukami, I'm
7 sorry. We're going to defer your and Dr. Curry's
8 question until later.

9 We're now going to take a 12-minute break, and
10 the committee will reconvene at 10:25 a.m. During the
11 break, panel members, please remember there should be
12 no discussion of the meeting topic during the break
13 amongst yourselves or with any member of the audience.
14 We will resume at 10:25. Thank you.

15 (Whereupon, at 10:12 a.m., a recess was
16 taken.)

17 DR. NEILL: By my watch, it's 10:25. Thank
18 you. We will now proceed with the FDA presentations.

19 **FDA Presentation - Sarah Arnold**

20 DR. ARNOLD: Good morning. I'm Sarah Arnold,
21 a medical officer from the Division of Anesthesia,
22 Analgesia, and Addiction Products. I will begin with

1 some background of over-the-counter nicotine
2 replacement therapy and brief regulatory history of
3 this application; next, a brief description of the
4 product with dosing and administration instructions. I
5 will give a brief overview of efficacy findings, and
6 Ms. Kate Meaker, our statistician, will go over more
7 detailed findings.

8 The first pivotal study is study A6431111. We
9 abbreviated the study name, and hereafter we will refer
10 to it as study 11. The second pivotal study is
11 study CO140121222102-SCCT, originally study NICTDP3038.
12 We abbreviated the study name, and here after we will
13 refer to it as study 38. I will then give a brief
14 overview of product safety in the controlled clinical
15 trials and finish with conclusions. All of these
16 topics are described in more detail in the background
17 document.

18 Nicotine replacement therapy, abbreviated as
19 NRT, started out as prescription products. In 1984,
20 Nicorette Gum 2 milligrams was approved for adjunctive
21 therapy to behavioral treatment. More NRT products
22 were approved in the early 1990s, including the

1 4-milligram Nicorette Gum and 4 different transdermal
2 products. These products all required prescriptions at
3 the time and were labeled as adjunctive IV treatments.
4 Minimal intervention or over-the-counter studies were
5 rare.

6 In order to switch from prescription to OTC,
7 applicants had to develop and test self-help materials
8 and conduct clinical trials that simulated an OTC
9 environment. These studies included all comers that
10 were self-selected and purchase the product. These
11 studies were designed to compare results to real-world
12 quit rates.

13 The continuing abstinence rates, abbreviated
14 as CAR, in weeks 2 through 6, would consistently fall
15 between 15 percent and 20 percent in the active group.
16 NRT development for direct OTC approvals involved
17 simulated OTC environments that were placebo controlled
18 and double-blinded. Applicants could also develop
19 PK-only programs if their drugs were similar enough to
20 another marketed product.

21 You have an account of the regulatory history
22 in your background package. Nicotine mouth spray

1 development began with a pre-IND meeting in 2007 during
2 which the agency gave advice on the drug development
3 program. Their traditional prescription like RCT was
4 completed in Europe; the OTC study completed at the
5 United States.

6 As noted in Dr. Kelty's overview earlier,
7 these are the studies and data submitted by the
8 applicant. The clinical development program consisted
9 of 9 studies, and Ms. Meaker and I will be focusing on
10 the phase 3 safety and efficacy studies.

11 This slide is a review of the product
12 description presented earlier, and this slide presents
13 an overview of the studies side by side. Some notable
14 differences are the number of subjects and the ratio
15 per treatment arm. Study 11 had 479 subjects, a 2 to 1
16 ratio of active to placebo subjects in 3 centers in
17 Europe. Study 38 had 1,198 subjects at a one-to-one
18 ratio of active to placebo in 8 centers in the United
19 States.

20 Drug availability to the subjects was also a
21 difference. In the first study, study 11, subjects
22 received their last supply of medication at week 20 and

1 were followed until week 52. In study 38, subjects
2 were able to request medication for the duration of the
3 study, which was 26 weeks.

4 Also, a difference was product training and
5 smoking cessation counseling. In study 11, subjects
6 were trained on the product and received smoking
7 cessation counseling, while on study 38, the conditions
8 mimicked the OTC environment and didn't include product
9 training or smoking cessation counseling.

10 The initial dosing regimen and instructions
11 were the same in both studies. Weeks 1 through 6, 1 to
12 2 sprays every 30 to 60 minutes, a maximum of 4 sprays
13 per hour or 64 sprays per day. Week 7 through 9
14 reduced the number of sprays per day so that by week 9,
15 the subject is down to half the average number of
16 sprays per day. Weeks 10 through 12 further reduced
17 the number of sprays per day no more than 4 sprays per
18 day by week 12.

19 The placebo spray was identical in appearance
20 and formulation, except it did not contain nicotine.
21 The placebo contained a small amount of capsaicin to
22 mimic the taste and produce a sensation in the oral

1 cavity similar to that of nicotine.

2 This slide displays key demographics of both
3 studies side by side. The population in study 11 was
4 mostly white, otherwise the groups were similar. This
5 slide displays some key baseline characteristics. Of
6 note, study 11 had a higher percentage of subjects who
7 smoked greater than or equal to 20 cigarettes per day,
8 and study 38 had a higher percentage of subjects who
9 smoked their first cigarette within 30 minutes of
10 waking.

11 These are two of the six questions which
12 comprise the Fagerstrom Nicotine Dependence Score.
13 Overall, the distribution of subjects' scores of the 0
14 to 10 scale were very similar in the two studies.

15 Ms. Kate Meaker, our statistical reviewer,
16 will now present efficacy results.

17 **FDA Presentation - Kate Meaker**

18 MS. MEAKER: Thank you, Dr. Arnold.

19 Dr. Arnold has explained the key differences
20 in the designs of study 11, the traditional clinical
21 study, and study 38, the OTC setting study. I will
22 discuss the efficacy of the two studies in terms of the

1 continuous abstinence rate from weeks 2 through 6 on
2 treatment. This was the primary efficacy outcome in
3 both studies.

4 The secondary endpoints in the two studies
5 were based on length of study treatment and follow-up,
6 so the time frames do not match. Regardless, the
7 results from the secondary endpoints were similar to
8 the results and conclusions from the primary time frame
9 of weeks 2 through 6.

10 First, I will show the results for the two
11 studies are notably different in terms of the magnitude
12 of the treatment effect, although both achieved
13 statistical significance. I will then discuss analyses
14 intended to investigate potential explanations for the
15 notable differences. Lastly, I will discuss the
16 clinical meaningfulness of the results.

17 This table shows the efficacy results for the
18 two studies of interest. The success rates are the
19 same as the results presented by the sponsor this
20 morning. In both studies, the treatment groups were
21 statistically significantly different as demonstrated
22 by a p-value of less than 0.05. I compare the

1 treatment groups using the differences in success rates
2 rather than odds ratios or relative risks.

3 Study 11 highlighted here is the traditional
4 clinical study. Subjects had more interaction and
5 instruction from the clinic staff, including how to use
6 the nicotine mouth spray dispenser and counseling for
7 quitting smoking. The overall difference in success
8 rates for continuous abstinence from weeks 2 through 6
9 was 10 percent in this study.

10 Study 38 shown on the right was designed to
11 more closely resemble the over-the-counter setting for
12 the desired indication. The subjects had no
13 instruction on product use or smoking cessation
14 counseling aside from what was provided on the carton
15 and label. The overall difference in success rates for
16 continuous abstinence from weeks 2 through 6 was 2.5
17 percent in this study, notably lower than abstinence
18 rates in study 11.

19 Here, I show the dropouts in the two studies.
20 Although the discontinuation rates were higher in
21 study 11 than in study 38, these are not uncommon rates
22 for smoking cessation studies of these durations. The

1 majority of dropouts in both groups in both studies
2 were due to withdrawn consent or lost to follow up,
3 also common in smoking cessation studies.

4 All subjects who discontinued from the study
5 are classified as non-responders for abstinence
6 endpoints. The first row shows discontinuation during
7 the time frame for the primary efficacy outcome. In
8 spite of the higher discontinuation rates in study 11,
9 study 11 still showed higher abstinence rates than
10 study 38. Thus, discontinuations did not account for
11 the lower abstinence rates in the OTC setting study.

12 We also considered if differences in the
13 patient populations who were enrolled in the two
14 studies could explain the low success rates. First, we
15 considered demographic characteristics of the enrolled
16 smokers. As shown here, the average age of the
17 subjects was 4 years higher in study 38, but the
18 abstinence rates were consistent across the age groups,
19 indicating age did not account for the lower rates in
20 the OTC setting. Study 38 had a higher percentage of
21 females than study 11, but the abstinence rates were
22 consistent across gender. So the low rates in the OTC

1 setting were not attributable to gender.

2 Study 11 was conducted in Germany and Denmark.
3 Study 38 was conducted in the United States and
4 enrolled higher proportion of people of color. The low
5 abstinence rates were consistent across the race groups
6 in the OTC setting study. We also considered aspects
7 of smokers' cigarette use at baseline. Study 38 had a
8 higher proportion of subjects who smoked more than
9 20 cigarettes per day.

10 Oh, I'm sorry. Study 38 had a higher
11 proportion of subjects who smoked less than 20
12 cigarettes per day. This is due to the design.
13 Enrollment in study 38 was stratified by the number of
14 cigarettes smoked at baseline to ensure that both
15 strata had equal sample size. But again, the low
16 abstinence rates in the over-the-counter study were
17 consistent regardless of baseline cigarette smoked.

18 As Dr. Arnold mentioned, the subjects in the
19 two studies were similar in terms of baseline
20 Fagerstrom Nicotine Dependence Score, a scale that
21 ranges from 0 to 10. The baseline Nicotine Dependence
22 Score does not account for the lower rates in the OTC

1 setting. And lastly, study 38 had a higher proportion
2 of subjects who smoked their first cigarette within
3 30 minutes of waking, but this did not account for the
4 lower abstinence rates in the OTC setting.

5 In summary, while the subjects enrolled in the
6 two studies were somewhat different, these differences
7 did not account for the low abstinence rates in
8 study 38, which was conducted in the United States and
9 specifically designed to more closely mimic the
10 over-the-counter experience for which the applicant is
11 requesting approval.

12 Earlier this morning, the applicant presented
13 the results of the same two efficacy studies, which I
14 have presented. The applicant focused on the odds
15 ratio and the relative risk. My analyses do not
16 contradict the applicant's results, however, I will
17 discuss the results in terms of the difference in
18 success rates. It better conveys the benefits in terms
19 of treatment effect size.

20 The difference in success rates can also be
21 used to evaluate risk-benefit when translated into the
22 number needed to treat. This is the number of subjects

1 who would need to be treated with the new treatment
2 instead of placebo in order to expect a single
3 successful outcome, i.e., a single smoker able to
4 achieve continuous abstinence from weeks 2 through 6.

5 In the traditional clinical setting,
6 number 11, with a higher level of interaction and
7 training from study staff, an average of 10 more
8 smokers would have to be treated with nicotine mouth
9 spray rather than placebo in order to expect one smoker
10 to successfully be abstinent from weeks 2 through 6.
11 In study 38, designed to mimic the over-the-counter
12 setting, an average of 40 smokers would need to be
13 treated with nicotine mouth spray instead of placebo in
14 order to expect one smoker to successfully be abstinent
15 from weeks 2 through 6.

16 As a general comparison, the Commit lozenge
17 nicotine replacement product was approved in 2002 based
18 on a direct-to-OTC clinical development plan with an
19 efficacy study which was similar to study 38 here.
20 Smokers who were provided the drug facts label and
21 package directions to determine which dose level of the
22 blinded study treatment, either low, 2 milligrams, or

1 high, 4 milligrams, would be most appropriate for
2 themselves.

3 As shown here, the abstinence rates, treatment
4 effect sizes, and number needed to treat for this
5 similar nicotine replacement treatment in a similar
6 randomized double-blind, over-the-counter setting
7 clinical study were notably better than what was
8 observed in study 38, or even study 11, of the nicotine
9 mouth spray being presented today.

10 Although the analyses of the two nicotine
11 mouth spray studies concluded statistically significant
12 differences, the clinical meaningfulness of the
13 treatment effects is questionable. Now, Dr. Arnold
14 will return to present the safety results for the
15 nicotine spray studies.

16 **FDA Presentation - Sarah Arnold**

17 DR. ARNOLD: Thank you, Ms. Meaker.

18 Since nicotine's safety profile is well
19 characterized, the focus of this safety review was on
20 formulation specific findings that might be relevant in
21 the risk-benefit assessment. Local irritation was a
22 particular concern, which was reviewed by our dental

1 consultant. This is relevant for both active and
2 placebo arms of the study because the placebo contained
3 capsaicin to mimic the taste of nicotine. Persistent
4 use was also a concern as a possible indicator of abuse
5 potential.

6 This slide shows the 9 studies supporting this
7 application. There were 1,526 total subjects exposed
8 to nicotine mouth spray in these 9 studies. Just to
9 review, the regulatory definition of serious adverse
10 events is as follows.

11 As per part 312.32, the Code of Federal
12 Regulations, an adverse event is considered serious if
13 in the view of either the investigator or sponsor, it
14 results in any of the following outcomes: death; a
15 life threatening adverse event; inpatient
16 hospitalization or prolongation of existing
17 hospitalization; or persistent or significant
18 incapacity; or substantial disruption of the ability to
19 conduct normal life functions; or a congenital anomaly
20 or birth defect.

21 There were no deaths reported in the phase 1
22 and phase 2 studies. There were a total of 8 deaths

1 reported in the phase 3 studies. The narrative
2 summaries were all reviewed and the deaths were
3 unlikely related to the study drug.

4 This slide presents nonfatal serious adverse
5 events. All the case report forms were reviewed and
6 none were found to be attributable to the study drug.
7 In study 11, 41 subjects withdrew because of adverse
8 events. In the placebo groups, 7 percent withdrew.
9 The most common reason was dyspepsia. In the active
10 group, 9 percent withdrew, and the most common reason
11 was nausea. In study 38, 40 subjects withdrew due to
12 adverse events. In the placebo group, 2.7 withdrew.
13 The most common reason was tooth abscess. In the
14 active group, 4 percent withdrew. The most common
15 reason was hiccups.

16 The most common treatment-emergent adverse
17 events in the active arm of both pivotal studies were
18 hiccups, headaches, and local mouth throat irritation.
19 Several common adverse events in the active arm of both
20 studies affected the gastrointestinal nervous systems,
21 which is typical for smoking cessation studies, such as
22 nausea, vomiting, heartburn, and dizziness.

1 This slide displays the top 10 most common
2 adverse events seen in greater than or equal to 2
3 percent of the active arm for study 11. This study
4 used a checklist that's specifically solicited for
5 these symptoms, which may have increased the reporting
6 rates. Adverse events were recorded for the full
7 52 weeks of the study. Findings of visual mouse
8 inspections were not included in the adverse events in
9 the case report forms.

10 This study also did not differentiate those
11 events which were considered treatment emergent from
12 those that weren't. By treatment emergent, we mean
13 they started or worsened while the person was on the
14 study drug or shortly after discontinuation. This may
15 also contribute to the high rate of reporting of common
16 events such as headache and common cold. I have a
17 separate analysis in the backup slides that looks only
18 at the first 12 weeks, and a few of these items do fall
19 out of the top 10 list.

20 This slide displays the top 10 most common
21 treatment-emergent adverse events greater than or equal
22 to 2 percent of the active arm for study 38.

1 Treatment-emergent events were defined in this study as
2 those adverse events with a relationship to study
3 medication of possible, probable, or very likely.
4 These were all spontaneously reported, so the reporting
5 rates are lower, but the general profile is the same as
6 study 11, with hiccups being a very common complaint.

7 Nicotine is a known local irritant, and
8 capsaicin, which was in the placebo, is also irritating
9 to the oral mucosa. In study 11, visual mouth
10 inspections were performed at baseline and weeks 2, 12,
11 and 24, and were not included in the adverse event
12 tabulations. In study 38, the visual mouth inspections
13 were performed by dentists or qualified dental
14 professionals at baseline and week 6. The findings
15 were included in the adverse event tabulations.

16 For study 11, one or more new oral
17 abnormalities or lesions were reported for 5.7 percent
18 of subjects in the active group versus 4.3 percent in
19 the placebo group. For study 38, 2.5 percent in the
20 active group and 1.2 percent in the placebo group who
21 had normal baseline exams developed abnormal lesions at
22 7 weeks. Also for study 38, for those subjects with

1 one or more abnormalities at week 6, 17.6 percent in
2 the active group and 9.8 percent in the placebo group
3 had a new or worsened oral condition.

4 As noted in the beginning of the presentation,
5 in study 11, the last medication supply was given at
6 the week 20 visit. In study 38, however, subjects were
7 permitted to use medication for the duration of the
8 study, which was 26 weeks, so we looked at persistent
9 use beyond the recommended dosing regimen.

10 For subjects who provided use data in study
11 38, at week 13, 92 percent of the active group were
12 continuing product use. At week 26, 78.8 percent of
13 the active group were continuing product use. Among
14 the 28 subjects who are abstinent at week 26 and
15 provided reports on their product use, 50 percent
16 reported that they were not using the study drug at
17 all. Twelve were using less than the recommended dose
18 and 2 were using more. This suggest that staying on
19 the study drug wasn't the only way to stay quit.

20 Among the 109 subjects who were non-abstinent
21 at week 26 and provided reports of their product use,
22 only 14 percent reported that they were not using the

1 study drug. The remaining 94 people reported ongoing
2 use, suggesting dual use of nicotine mouth spray in
3 cigarettes. These data weren't reported for the
4 placebo group.

5 So in conclusion, study 11 provides evidence
6 that under the right circumstances, nicotine mouth
7 spray can be more effective than placebo in helping
8 smokers quit. However, the results of study 38
9 suggests that the translation of the product for
10 stand-alone use in OTC conditions in United States
11 consumers was not successful.

12 Nicotine mouth spray is associated with
13 hiccups, local or mucosal irritation, including new
14 abnormalities, in addition to the typical NRT adverse
15 events such as nausea, vomiting, dizziness, and
16 headaches. Persistent use among non-quitters was more
17 likely than successful quitting.

18 **FDA Presentation - Martha Lenhart**

19 DR. LENHART: Good morning. My name is Martha
20 Lenhart. I'm a medical officer in the Division of
21 Nonprescription Drug Products. Today, I will present a
22 postmarketing safety data review of nicotine mouth

1 spray. This presentation includes an overview of
2 postmarketing data constructs such as database
3 limitations and terminology and results of database and
4 literature searches. Note, the abbreviations for the
5 applicant's global safety database as GSD and the FDA
6 adverse event reporting system as FAERS.

7 For search results of the review, it's
8 important to keep in mind that findings in
9 postmarketing safety databases are limited by the
10 spontaneous reporting of adverse events, and analyses
11 of these data are constrained by content typical of
12 spontaneous reporting.

13 For example, reports are voluntarily submitted
14 by a variety of individuals, including consumers and
15 practitioners. Clinical information is often limited
16 and incomplete. And over time, events may be less
17 frequently reported. Additionally, reporting may be
18 biased with the reporter's intent potentially
19 confounding the association between use of a drug and
20 reported adverse event.

21 As a reminder, adverse events are defined by
22 the FDA as any untoward medical occurrence associated

1 with the use of a drug in humans whether or not the
2 drug is considered related to the event. So an adverse
3 event can be any unfavorable and unintended sign,
4 symptom, or disease temporally associated with the use
5 of a drug product.

6 When categorizing adverse events, some events
7 are more worrisome than others, and these are
8 categorized as serious adverse events. The FDA
9 definition of a serious adverse event is any adverse
10 drug experience occurring at any dose that results in
11 any of the outcomes listed here. Development of drug
12 dependence or drug abuse is considered serious because
13 these may require medical intervention to prevent one
14 of the outcomes listed.

15 The potential for abuse or misuse is an
16 important consideration for medications used in
17 over-the-counter settings. Definitions of drug abuse
18 and misuse are described in the FDA guidances and
19 provided here. These descriptions are also included in
20 table 31 of the backgrounder. Drug dependence as a
21 physical or psychological dependence is also described
22 in FDA guidances and also provided in table 31 of your

1 backgrounder.

2 In terms of a database searches and for a bit
3 more background, the preferred term "drug dependence"
4 was introduced in 1999 in the Medical Dictionary for
5 Regulatory Activities, MedDRA version 2.1. For more
6 specificity, nicotine dependence became a preferred
7 term in 2003 in MedDRA version 6.1.

8 However, detailed patient information about
9 dependence, nicotine dependence, and drug dependence is
10 not intrinsically included in the databases, making it
11 difficult to confirm exact differences among reports.
12 Examples of abuse, misuse, and dependence reporting
13 will be provided later in the database search results.

14 As we note, marketing history of nicotine
15 mouth spray begins in the United Kingdom in 2010.
16 Nicotine mouth spray is currently approved and marketed
17 in many countries. The mouth spray is available as
18 either a behind-the-counter prescription product or a
19 front-of-the counter general sales product, which is
20 similar to our over-the-counter status. In the UK, as
21 previously noted, nicotine mouth spray is a
22 front-of-the counter product and is labeled for use

1 down to the age of 12. At present, the mouth spray is
2 not approved for use in any status in the United
3 States.

4 Turning to the applicant's pharmacovigilance
5 database for adverse events associated with the spray
6 formulation of nicotine, the applicant submitted
7 analyses of 7 and a half years of postmarketing
8 reports. The applicant's presentation earlier, you may
9 note, showed more cases, and this is due to a longer
10 span of data collection. However, these differences
11 don't change the overall conclusions.

12 The GSD adverse event data associated with
13 internationally marketed nicotine mouth spray consists
14 primarily of an adult population. There were
15 approximately 4600 case reports having 9800 adverse
16 events, indicating in some instances more than one
17 adverse event reported per case. 450 of the cases were
18 categorized as serious.

19 The 450 GSD serious cases reported 1143
20 adverse events. In total, terms related to dependence
21 account for 293 of these cases. The applicant's
22 submission concludes that this is reflective of

1 underlying dependence on nicotine, and the applicant
2 considered most of these serious cases due to a
3 transfer dependence rather than dependence specific to
4 nicotine mouth spray use.

5 In 43 cases describing smokers trying to
6 overcome their tobacco dependence, 19 were classified
7 as misuse and 24 as overdose cases. These were
8 associated with use of nicotine mouth spray more often
9 or longer than recommended. Only one of the misuse
10 cases lists characterized as abuse.

11 The applicant identified 4100 non-serious
12 cases with 8600 adverse events. The table on the left
13 was the most commonly reported events in non serious
14 cases. Hiccups, oral discomfort, and throat irritation
15 comprised most local events and contributed to 26
16 percent of non-serious event reports. Hiccups
17 represented the only event in 6.8 percent of the case
18 reports.

19 The applicant identified 15 percent of the
20 events were related to product handling, including
21 quality issues, device malfunction, and medication
22 error. Nausea and vomiting were among 12.7 percent of

1 the systemic events.

2 Demographically, the global safety database
3 search results showed similar numbers of gender-related
4 serious and non-serious events. The pediatric subgroup
5 had no reported serious adverse events, and additional
6 details of this subgroup are provided on the next
7 slide.

8 Among cases reporting age, there were only 16
9 with the use of nicotine mouth spray in the pediatric
10 subgroup. No serious cases were reported as mentioned
11 previously. In 12 of these cases reporting in age, one
12 was of an infant, 8 children, and 7 adolescents with
13 7 females and 6 males included.

14 Some of the cases related to a 2015 UK
15 newspaper article reporting that nicotine spray issued
16 to a 12-year-old girl was shared with a group of 20
17 classmates. The news release noted students became
18 nauseated, having symptoms of vomiting, dizziness, and
19 headaches. And in one case, a student needed hospital
20 treatment that was not further described. Overall, the
21 adverse events reported in this population are known
22 and consistent with the non-serious adverse events of

1 the adult population.

2 In assessing postmarketing safety through
3 other databases, the FDA's Division of
4 Pharmacovigilance conducted FAERS and VigiBase searches
5 to identify case reports of nicotine mouth spray. 166
6 FAERS reports were retrieved, and after applying case
7 definitions and accounting for duplicate reports,
8 96 cases were included in the case series. The
9 VigiBase search retrieved 180 cases, though it's
10 possible that some VigiBase reports may be duplicates
11 of the FAERS cases.

12 As a point of clarification, non-U.S. marketed
13 drug product reports may appear in FAERS when directly
14 reported by an international sponsor or in cases when
15 an international adverse event reported with multiple
16 drugs that include a U.S. marketed product, and in this
17 instance, nicotine mouth spray as well. The
18 demographic results in both FAERS and VigiBase searches
19 show similar gender case report distributions and
20 slightly more consumer reporting to the WHO database.

21 This table lists the top 5 serious adverse
22 events from FAERS and VigiBase searches. These serious

1 adverse events were similar across both data sources.
2 Our classification of cases as abuse, misuse, or
3 dependence is described in the next slides.

4 In classifying cases as drug abuse, misuse, or
5 drug dependence, we use the criteria of presence of one
6 or more of these terms in a report narrative or the
7 Division of Pharmacovigilance reviewers' clinical
8 assessment of a case narrative. Using these criteria,
9 FAERS narrative reviews resulted in classification of
10 26 cases as dependence, misuse, or abuse. These
11 occurrences were not mutually exclusive in that some
12 cases were classified with a combination of the terms,
13 and narratives were not available for the VigiBase
14 cases.

15 In the misuse cases, 12 of 18 described use of
16 nicotine mouth spray for longer than labeled duration,
17 reporting a range of 3 months to 5 and a half years.
18 Eight described the use of nicotine mouth spray at
19 higher doses than labeled. Examples of abuse cases
20 included, as mentioned in the applicant's presentation,
21 a pharmacy assistant who intentionally misused nicotine
22 mouth spray to, quote, "have a little fun," and

1 experienced an asthma attack. And another example of
2 abuse was that of a 60-year-old female who was using
3 the nicotine mouth spray too often.

4 To examine dependence associated with other
5 oral nicotine replacement products, we searched for
6 adverse events of gum and lozenge products. We chose a
7 5-year time frame to account for reporting biases such
8 as potential decline in reports over time after
9 regulatory approval.

10 In all three searches, either drug dependence
11 associated with the prescription and OTC
12 over-the-counter gum, or nicotine dependence associated
13 with the over-the-counter lozenge, ranked among the top
14 3 event terms reported. These terminology variances
15 can be related to the introduction of new terms with
16 MedDRA updates.

17 In our literature search of articles relevant
18 to nicotine mouth spray, we identified 14 publications.
19 Five of them discussed studies involving a 12-week
20 nicotine mouth spray treatment arm. Three of these
21 publications summarized clinical trial data used to
22 support the product application. Six of the articles

1 identified here highlight adverse events associated
2 with nicotine mouth spray specifically and oral
3 nicotine replacement products in general.

4 To summarize the postmarketing safety results,
5 dependence was the most common serious adverse event
6 identified in database searches. Hiccups represent the
7 most common non-serious event reported for nicotine
8 mouth spray, and published literature show a general
9 adverse event similarity of nicotine mouth spray to
10 other oral NRTs, meaning the same types of adverse
11 events were reported, although the frequencies were
12 different, with hiccups primarily associated with a
13 nicotine mouth spray use.

14 In conclusion, postmarketing safety findings
15 from pharmacovigilance database and literature searches
16 show a safety profile of nicotine mouth spray similar
17 to existing formulations of oral nicotine products
18 marketed as NRTs.

19 **FDA Presentation - Barbara Cohen**

20 MS. COHEN: Good morning. I'm Barbara Cohen,
21 a social scientist in the Division of Nonprescription
22 Drug Products, and I'm going to be presenting today on

1 the label comp study for the nicotine mouth spray.
2 Before I get into the specifics of this particular
3 study, I would like to spend a couple of minutes
4 speaking about nonprescription label comprehension
5 studies in general since some of you may be unfamiliar
6 with them. I'll then turn to the applicant's label
7 comprehension study number 181093, its objectives,
8 design and conduct, and results and finally close with
9 a summary.

10 What is the label comprehension study, or LCS,
11 as we commonly refer to it? For OTC products, the drug
12 facts label, or DFL, contains the critical information
13 that consumers need to know for safe and effective use
14 of the product. Here, for instance, is the proposed
15 DFL for the nicotine mouth spray. The indication and
16 warnings are on the outer label, and when the yellow
17 part is peeled back, the all important directions for
18 use are displayed on the back of this outer label.

19 Label comprehension studies assess the extent
20 to which consumers understand the information on the
21 DFL and then apply this information to the situation of
22 a hypothetical third-party individual. They are

1 conducted for most nonprescription NDAs, whether they'd
2 be Rx to OTC switches or direct to OTC, as the pivotal
3 LCS is considered to be a foundational study and a
4 consumer behavior studies program. That's because if
5 people don't understand the basic elements of the
6 label, they will have even more difficulty applying it
7 to their own personal medical situation should they
8 potentially be interested in using the product.

9 Label comprehension studies address such
10 questions as is the wording understandable to the
11 average consumer and does it convey the key concepts
12 required for safe and effective use of the product?

13 As discussed in FDA's label comprehension
14 guidance for nonprescription products, all LCS studies
15 should identify the key communication objectives that
16 need to be understood by the consumer in order to
17 safely and effectively use the product, and applicants
18 should construct a questionnaire that targets
19 comprehension of these objectives in an unbiased way.
20 Any new statements that don't appear on other OTC drug
21 facts labels should be assessed.

22 Finally, test labels should be as close as

1 possible to the planned final labeling to obtain an
2 accurate picture of what consumers picking the product
3 up off the shelf would understand.

4 Primary objectives are the most important
5 communication objectives with target thresholds being
6 established a priori. These target thresholds are
7 based on the clinical implications for the consumer if
8 they fail to accurately understand the labeled items.
9 Adequate comprehension is assessed by comparing the
10 establish thresholds with the lower bound of the
11 two-sided 95 percent confidence interval.

12 Typically, LCS thresholds range from 90
13 percent, representing endpoints of the most serious
14 clinical concern, to 80 percent, which are of
15 importance but not as clinically concerning. Most
16 importantly, nonprescription thresholds are targets
17 rather than hard stops that would be the basis for a
18 regulatory non-approval decision.

19 What I mean by this is that if a study
20 population approaches the target threshold but doesn't
21 quite need it, we try to gain some insights as to why.
22 What could be improved with the label that could

1 potentially get people over that threshold? Secondary
2 objectives are label statements that are less critical
3 to safe and effective use but are still critically
4 relevant. Typically, however, they are not assessed
5 against thresholds; only point estimates are reported.

6 Next, a word about literacy considerations.
7 FDA generally asks for a 25 to 30 percent limited
8 literacy representation in the study population. The
9 average reading level in the United States is estimated
10 at the 8th grade, so we ask that the DFL be written
11 ideally at a 4th to 8th grade reading level, and
12 limited literacy participants should be consumers with
13 4th to 8th grade reading levels as assessed by
14 validated instruments such as the REALM, which is the
15 rapid estimate of adult literacy in medicine.

16 Recruitment for LCS studies is typically from
17 an all comers population, meaning that there is minimal
18 screening involved, and participants don't need to
19 necessarily experience the medical condition to take
20 part in the study, however, targeted recruitment is
21 appropriate at times.

22 Typically in LCS interview, participants are

1 recruited through marketing research site databases,
2 and appointments are made for them to come in for a
3 1-on-1 interview. They go to the research facility,
4 and after the consent forms and the REALM are
5 administered, they are asked to read the label at their
6 own pace. Then the interviewer essentially administers
7 an open-book test to assess whether they understand the
8 label, meaning that they can always go back to the
9 label, refer back to it when answering a question.
10 This is not a test of memory. It's a test of being
11 able to see and comprehend the words when they are
12 being presented to the participants.

13 Typically, third-party scenarios are presented
14 so that the participants can apply the information
15 presented in a more neutral way rather than thinking
16 about what they themselves would do in a particular
17 situation.

18 Now, I'll turn to the label comprehension
19 study that the applicant conducted as part of this NDA
20 submission. There were four primary objectives, and
21 they were each assessed at an 80 percent target
22 threshold. These were comprehension of: 1) do not

- 1 inhale when spraying; 2) rinse immediately with water
- 2 if you spray in eyes as irritation will occur;
- 3 3) step 1, maximum number of sprays per hour, 4;
- 4 4) step 1, maximum number of sprays per day, 64.

5 There were eight secondary objectives. These
6 were comprehension of:

- 7 1) step 1, use 1 to 2 sprays when you would
8 normally smoke a cigarette or have a craving to smoke;
- 9 2) step 1, use the second spray if your
10 cravings are not reduced within a few minutes;
- 11 3) for best results, do not swallow for 2 to
12 3 seconds after spraying;
- 13 4) step 2, start reducing the number of sprays
14 per day;
- 15 5) step 2, by the end of week 9, you should be
16 using half the average of sprays per day that you used
17 in step 1;
- 18 6) step 3, continue reducing the number of
19 sprays per day so that you are not using more than
20 4 sprays per day during week 12;
- 21 7) to increase your chance of success, it is
22 important to use the nicotine mouth spray according to

1 the 12-week schedule;

2 8) when using this product, hiccups or minor
3 mouth and throat irritation may occur. Stop use and
4 ask your doctor if these products persist or worsen
5 during the course of treatment.

6 This study was conducted in September 2018 in
7 10 geographically dispersed sites across the country
8 with a total of 504 participants, males and females,
9 ages 18 plus. A total of 130 limited literacy
10 participants comprised 25.8 percent of the population.
11 All participants were either currently smokers or
12 attempting to quit. Of note, the LCS did not include
13 an additional untested statement that the applicant
14 subsequently added to the label, "Do not eat or drink
15 for 15 minutes before using this spray or while using
16 the spray."

17 Here are the results. This table displays
18 each primary objective along with the point estimate
19 percentage of overall correct responses for the total
20 study population, the confidence interval and then the
21 normal literacy and limited literacy breakouts. As the
22 table illustrates, most objective scored well, but I've

1 highlighted in bold the one outlier; rinse immediately
2 with water if you spray in eyes.

3 There you can see that not only the total
4 study population scored under 74 percent as the lower
5 bound, but the point estimates for normal literacy and
6 limited literacy were very similar. This is somewhat
7 unusual, as typically there is more of a substantial
8 difference between these two subgroups, and it's an
9 indicator that something could be amiss.

10 Now to the secondary endpoints, we've grouped
11 6 of the 8 endpoints into two separate themes for
12 clarity purposes. The first thematic grouping is what
13 we call general use. This table represents the same
14 array is that for the primary endpoints with the
15 exception of no-confidence intervals since the
16 secondary endpoints are not subject to the thresholds.
17 Here, we're looking at point estimate only.

18 Here you can see that the secondary endpoints,
19 for best results do not swallow for 2 to 3 seconds
20 after spraying, and step 1, use the second spray if
21 your cravings are not reduced within a few minutes, did
22 very well on comprehension, both overall and within

1 normal literacy and limited literacy. Overall, for
2 instance, they had scores of 93.7 percent and
3 93.1 percent, respectively.

4 For the objective of hiccups or minor mouth
5 and throat irritation may occur, stop use and ask a
6 doctor if these problems persist or worsen over
7 treatment, the comprehension was lower, overall at
8 81.2 percent with a normal literacy score of
9 83.2 percent and a limited literacy score of
10 75.4 percent. This is not a poor score per se, but if
11 users don't realize that hiccups or minor mouth and
12 throat irritation could be a normal side effect, it
13 could deter them from continuing with the therapeutic
14 regimen as outlined.

15 Our second thematic grouping is the
16 comprehension of the key dosing steps in timing: step
17 1, use 1 to 2 sprays when you would normally smoke a
18 cigarette or have a craving to smoke; step 2, by the
19 end of week 9, you should be using half of the average
20 number of sprays per day that you used in step 1; and
21 step 3, continue reducing the number of sprays per day
22 so that you are not using more than 4 sprays per day

1 during week 12.

2 Here you can see the decrease in comprehension
3 over the time sequence. People have a very good
4 understanding of step 1, then it begins to fall for
5 step 2, and importantly, this objective for step 2 only
6 assess comprehension of where people should be at the
7 end of the step, but it did not assess comprehension of
8 when they should start step 2.

9 Finally, we can see that it significantly
10 falls for step 3 in both the normal literacy and
11 limited literacy populations. Here, overall
12 comprehension decreases to 67.1 percent, with normal
13 literacy at 68.7 percent and limited literacy at
14 62.3 percent.

15 FDA then analyzed how many in this study
16 population had correct comprehension of all three of
17 the secondary objective steps related to dosing and
18 timing; plus for step 1, we also incorporated
19 comprehension of the primary objectives involved
20 regarding maximum number of sprays per hour, 4, and
21 maximum number of sprays per day, 64.

22 Here, we can see that of the total population,

1 only 48 percent correctly comprehended These two
2 primary objectives that I just mentioned, along with
3 the three relevant secondary objectives, with only
4 35.4 percent of limited literacy respondents being able
5 to comprehend all of these dosing steps.

6 In conclusion, for most objective, study
7 participants scored reasonably well on comprehension.
8 However, the additional statement on the DFL added
9 later presents an unknown factor. Additionally, the
10 relatively low comprehension among all, rinse
11 immediately with water if you spray into eyes as
12 irritation occur, may call for different placement or
13 highlighting on the DFL. Currently, it appears in the
14 middle of the direction section.

15 Moreover, as we just saw, understanding the
16 multiple dosing directions for different times in the
17 course of therapy may be problematic for consumers.
18 Both normal literacy and limited literacy consumers
19 scored low on comprehension of step 3, and that drove
20 low comprehension of all three steps together.

21 It is unclear how significant an issue this
22 is. The DFL has two relevant statements. First, under

1 directions, it states that to increase your chance of
2 success, it is important to use the nicotine mouth
3 spray according to the following 12-week schedule.
4 Secondly, at the bottom of the directions section and
5 bolded, it states, "Nicotine mouth spray is a medicine,
6 and it must be used in a certain way to get the best
7 results." Therefore, the impact of the relatively low
8 comprehension of the different dosing directions on
9 potential efficacy is unclear, and we leave that to
10 your discussion. Thank you.

11 **Clarifying Questions**

12 DR. NEILL: Thank you.

13 We are once again a bit ahead of schedule. By
14 way of explaining the process, what I'd like to ask for
15 are clarifying questions for FDA staff. I still have
16 four questioners with questions for GSK.

17 Depending on the timing, we're going to ask
18 clarifying questions until but no longer than 12 noon,
19 at which time we will break for lunch. If there are
20 questions that remain for either FDA or GSK, we will
21 address those this afternoon at an appropriate time.
22 So don't feel that you won't have an opportunity.

1 Just as with earlier, if you do have a
2 question, please keep your hand raised until Dr. Chee
3 can recognize you. So we've seen Dr. Parker,
4 Dr. Hatsukami, Maria -- I beg your pardon, Christianne,
5 and Neil. Let's begin with Dr. Parker.

6 DR. PARKER: I had a question about what we
7 used to call self-selection studies and the need to be
8 able to walk in without the learned intermediary and
9 say, is this product right for me? With this in
10 particular, I'm curious about that; like, how many
11 people would choose this or pick it up and be able to
12 look at some of the -- I think I'm reading them, but I
13 need to look at them under bigger magnification or
14 something.

15 For example, if I'm breastfeeding, if I'm
16 pregnant, if I had a heart attack two weeks ago, if I
17 have seizures, those are under the sort of talk to
18 somebody, but how many people would selectively pick
19 these up and not be aware that those are there, and if
20 we have any data on that or any need for data on that
21 in terms of self-selection. That's one of my
22 questions.

1 Then more broadly, whether or not there are
2 data about how many non-tobacco product users use
3 nicotine replacement products more broadly, because
4 that's part of my thinking behind that. Thank you.

5 DR. KELTY: Hi. This is Jenny Kelty, and I'll
6 go ahead and answer the first question regarding
7 self-selection. For this application or the
8 development program, we did not require a
9 self-selection study given that the NRT products,
10 multiple, are already out there, and the
11 well-established indication. The warnings are not new
12 in this proposed labeling, so it was not required to
13 conduct a self-selection study.

14 DR. PARKER: So it would be safe to say that
15 we have no data, and no data are available about how
16 many people self-select an NRT product who are not
17 smokers? There's no data available.

18 DR. KELTY: We do not have that data.

19 DR. NEILL: Anybody from FDA care to answer
20 Dr. Parker's second question?

21 DR. WINCHELL: I'm Celia Winchell from the
22 Division of Anesthesia, Analgesia, and Addiction

1 products. I can tell you that surveys on the use of
2 NRTs by non-smokers have customarily focused on the use
3 by minors. And the products that were available the
4 last time this survey was undertaken were gum, patch,
5 and to a lesser degree lozenge, many of which are
6 deliberately unpalatable. And at that time, I believe
7 the conclusion was that it was not at all common for
8 non-smoking youth to take up nicotine replacement
9 products, although it was not unheard of.

10 I think it's safe to say that the landscape
11 has changed quite dramatically in the last even two or
12 three years. It would be hard to draw any conclusions
13 about how appealing nicotine products are to
14 non-smokers now.

15 DR. NEILL: Thank you. Dr. Roumie?

16 DR. ROUMIE: I have two questions. The first
17 is for Ms. Meaker. You did many subgroup calculations
18 to try to understand the underlying efficacy results of
19 the 38 study, I believe. The question was, I believe
20 that the industry had obtained dosing information, and
21 did you look at a relationship between the dose
22 consumed and their likelihood of quit?

1 MS. MEAKER: This is Kate Meaker from the FDA,
2 statistical reviewer. We did look at the relationship
3 between product use and quitting. The product use was
4 classified as -- we divided it into two groups,
5 participants who used the correct, or at least the
6 correct amount, or those who used less than, assuming
7 that less than was ineffective. The low number of
8 smokers who actually quit in that study made it
9 difficult to suss out any real meaning from that
10 analysis, a lot of flat lines that didn't separate.

11 DR. ROUMIE: Thank you. The second question
12 is for Ms. Cohen. We heard about the timeline for the
13 original testing of the drug facts label and how some
14 of the aspects that we're looking at now may be
15 different. How similar or different do you feel, with
16 the exception of the one question that you pointed out,
17 is the testing of the drug facts labels that they
18 conducted to what they are putting forward now as their
19 revised version?

20 MS. COHEN: I'm sorry. Could you clarify the
21 question a bit?

22 DR. ROUMIE: So the question is, how similar

1 or different do you think the drug facts label that
2 they tested and got this data from is to what they are
3 putting forward now?

4 MS. COHEN: Well, they did test the label that
5 they are putting forward, with the exception of the
6 one --

7 DR. ROUMIE: The one question.

8 MS. COHEN: -- yes.

9 DR. ROUMIE: Thank you.

10 DR. NEILL: Thank you. Dr. Hatsukami?

11 DR. HATSUKAMI: I have a question for
12 Ms. Meaker. The problems of smoking is really highest
13 among the individuals that are of lower SES here in the
14 United States, and certainly with that population,
15 there's lower resources available to them. I was
16 wondering if there might be some differences, whether
17 you even have the information, to see if there are
18 differences in terms of the problems of lower SES folks
19 in the 38 versus the 11 study.

20 MS. MEAKER: We did not collect the
21 information that would be needed to define
22 socioeconomic status. We typically look at subgroups

1 by age, race, gender, and regional, and in study 38, we
2 had the literacy information that Dr. Cohen reported.
3 But aside from that, we don't look at that.

4 DR. HATSUKAMI: I have a couple of other
5 questions. One is whether you consider reach as an
6 important factor; that is, when you have an
7 over-the-counter product, it's a lot more accessible to
8 individuals versus going in to see a physician to get a
9 product. When you do the calculation in terms of
10 impact, do you consider reach of the product?

11 MS. MEAKER: No. We based our analyses just
12 on the clinical data, the clinical studies that were
13 conducted and submitted as part of the application.
14 It's not -- that would be more of an epidemiologic
15 reach, I believe, or study to project from the clinical
16 studies to --

17 DR. HATSUKAMI: To see how many people might
18 actually be affected, over the counter versus --

19 MS. MEAKER: -- yes.

20 DR. HATSUKAMI: Okay. The other question that
21 I have is, actually, how about looking at absolute
22 numbers. You say that there's only a 3 percent

1 difference between the placebo versus the active
2 medication, but the denominator's so high. I mean,
3 we're talking about 34 million people in the United
4 States that smoke; 17 million that try to make a quit
5 attempt.

6 So the denominator is high. So I'm wondering,
7 even though it's only 3 percent difference in terms of
8 the absolute number of people that might be affected,
9 that might be somewhat significant. So do you take
10 into consideration --

11 MS. MEAKER: Again, our role and regulatory
12 limitations are the clinical data submitted, but I
13 think that that question speaks more to what the
14 committee is going to look at this afternoon.

15 MR. PETULLO: This is David Petullo. That is
16 something we would take into account, but Kate's only
17 looking at the clinical trial that was conducted, and
18 part of the risk-benefit. We wouldn't --

19 MS. MEAKER: Take into account.

20 DR. HATSUKAMI: Okay, yes. Thank you.

21 DR. NEILL: Dr. Michele, did you want to
22 augment that response?

1 DR. MICHELE: No, I was going to say the same
2 thing.

3 DR. NEILL: Very good. Dr. Farber, and then
4 Dr. Curry?

5 DR. FARBER: So I have a question for
6 Dr. Cohen and a request for Dr. Nides; the first one
7 for Dr. Cohen.

8 In the label comprehension study, I had seen
9 that there was -- sorry. This is Neil Farber, UC San
10 Diego. I had seen that there was about a quarter of
11 patients who did not open the flap, and I was wondering
12 if there were any data looking at the differences in
13 comprehension from those who did or did not open the
14 flap.

15 MS. COHEN: Yes. I have a backup slide on
16 that. I don't know if we could go to my backup slides.
17 But there were some differences for some of the
18 elements. It's a little hard to really get at the
19 implications of that because there are some study
20 artifacts as well.

21 In other words, for people who didn't open the
22 flap, they had a lower comprehension. So that could be

1 a concern if people never actually in real life open
2 the flap to look at the directions for use. This flap
3 is a bit unusual in that you do have to peel it over,
4 and there are those important directions on the other
5 side. Not every product has that.

6 But at the same time, there were some study
7 artifacts. Some people, the interviewers asked why
8 they didn't open the flap, they said, well, I was
9 afraid to tear the product or something, or damage the
10 product in some way. So that plays into it, too, in
11 terms of why they didn't open it to begin with. But
12 that being aside, there were some differences.

13 Do we have the backup slide? I was told to
14 ask for those. I don't have it on the official -- you
15 can just go to my backup slides. I think this was the
16 only one with data on it.

17 So here we can see for those who did not open
18 the DFL until prompted, there was a lower of a score
19 with the rinse immediately and also particularly with
20 maximum number of sprays per day, 64 per day. But
21 again, we don't know for sure whether they would have
22 done it in real life, and we're just afraid to open it

1 in the context of the study.

2 DR. FARBER: And for Dr. Nides, you had
3 mentioned, when I was asking earlier about the
4 difference in number of patients who continued smoking
5 in the lozenge trial versus the nicotine mouth spray
6 trial, you said that basically there were studies
7 looking at both patches and gum that had data similar
8 to those of the nicotine mouth spray. If you could
9 provide those data, please, so that I could see that
10 they're similar.

11 DR. NEILL: I apologize. I did not realize
12 you were asking sponsor for data.

13 Having asked, and given that we're also
14 looking for data from Dr. Parker's earlier question,
15 did you understand Dr. Farber's request?

16 DR. NIDES: Yes.

17 DR. NEILL: Perfect. If you could collect
18 those, we we'll present those as well when we come back
19 to sponsor's clarifying questions. Dr. Curry?

20 DR. CURRY: Thanks. I appreciated all the
21 work that you did to try to understand the differences
22 in quit rates between the two studies. I'm going back

1 to really the first question because I'm still trying
2 to figure out, on page 42 of the FDA briefing document,
3 compliance with study drug.

4 I've read this paragraph several times. I
5 think it means that there wasn't an association between
6 the use of the active mouth spray and whether or not
7 people were quitting. I'm a little bit confused by
8 that. So can someone interpret that for me? It refers
9 to a table 64, which I couldn't find in the applicant's
10 materials. But it basically says that subjects who
11 were successful quitters on active NMS were even more
12 likely, than unsuccessful quitters, to use the spray
13 less than recommended, and were more likely than
14 non-quitters to report using no doses in a given week.

15 So I'm trying to put all this together. Maybe
16 half of the folks even understood how to use all of the
17 medication. You're seeing higher quit rates in the
18 active medication group but evidence of less medication
19 use.

20 DR. WINCHELL: Let me take a quick crack at
21 this. Your confusion is understandable, and one of our
22 first attempts to understand the difference between the

1 two studies was to delve into is it possible that
2 people in a European study understood how to use the
3 product, and that's why they were successful because
4 they followed the directions; and they used the amount
5 they were supposed to use and that's why they were
6 successful; and the people in the American study did
7 not understand, and it's all explained right there.

8 Using the data we had available to us, which
9 in some cases was limited to just the people on active
10 or just the people who were abstinent, we did not find
11 that to explain the difference. And I think that
12 Ms. Meaker explored that, and as she mentioned before,
13 the low number of successful quitters made it hard to
14 draw conclusions. But let me see whether she had more
15 to say about that.

16 MS. MEAKER: This is Kate Meaker. So are you
17 asking about use over time?

18 DR. CURRY: So if you have an over-the-counter
19 medication that's going to help you quit, one might
20 assume that if you use it more, you're more likely to
21 quit. And that's what I'm trying to find. There was
22 just one little paragraph on compliance, so maybe we

1 can't answer the question. I mean, it is low quit
2 rates and so forth, but I just wanted to make sure that
3 I read that paragraph correctly; that there was less
4 use -- I mean, there might be less use over time
5 because people use it, they quit, so they stop using
6 it -- I mean, that's a good thing -- or there may be
7 less use over time because people are quitting some
8 other way. I'm just trying to understand a little bit
9 better.

10 MS. MEAKER: Okay. The percentage of subjects
11 in both groups -- and this is study 38. The percentage
12 of subjects in both groups, regardless of whether it
13 was consistent across time, if you were
14 classified -- so we classified all subjects as either
15 successful on that primary endpoint, weeks 2 through 6,
16 or not.

17 The correct or incorrect use was consistent
18 across each of those subgroups. So of the 4 subgroups
19 by treatment and by whether or not they used correctly
20 or not, if it was approximately, if it was in the 75 to
21 80 percent range at the beginning, it stayed that way
22 over time.

1 DR. NEILL: Thank you. I have a question for
2 FDA. This is Richard Neill. In the proposed drug
3 facts label, there's no language that I can find that
4 says stop using this after 12 weeks, as a part of this
5 12-week program. There is language -- and I'm looking
6 at sponsor packet, page 63, the proposed drug facts
7 label, that says, "It's important to complete
8 treatment. If you feel the need to use Nicorette Quick
9 Mist Mouth Spray for a longer period to keep from
10 smoking, talk to your health provider."

11 What I'm asking FDA is, how congruent that
12 labeling is among other nicotine replacement therapy,
13 and can you help me with my challenge as a physician,
14 which is when we're trying to get people to stop
15 smoking, we say stop smoking. When we're trying to get
16 people off nicotine replacement, we say stop using.
17 And it's just striking that nowhere in this does it say
18 stop using this. So if you could elaborate.

19 DR. WINCHELL: Sure. I'll take that. This is
20 Celia Winchell. That is actually consistent with the
21 current labeling of these products. Several years ago,
22 we undertook an evaluation of the risks and benefits of

1 long-term use of nicotine replacement products, and
2 while we did not find there was evidence to
3 affirmatively recommend that people use NRT long term,
4 we also found that there were some individuals whose
5 long-term abstinence from cigarettes was maintained by
6 virtue of their ongoing use of Nicorette or other NRT
7 products, at a usually low and sporadic level.

8 When we didn't think that would be harmful, we
9 issued a Federal Register notice, actually, explaining
10 that rather than saying stop use after 12 weeks, we
11 would like the label to say you should be sure to
12 finish the course, and if you felt you needed to use
13 more, you should your doctor. So that is consistent
14 with current labeling.

15 It is our hope and expectation that it would
16 be individuals who had successfully quit smoking and
17 felt the need for ongoing nicotine replacement who
18 would use these products over the long term and not
19 people who had not successfully quit smoking, and maybe
20 wouldn't be benefiting them.

21 DR. NEILL: Richard Neill. Does FDA consider
22 that a transfer of dependence, and is transfer of

1 dependence a serious adverse event as is development of
2 drug dependence?

3 DR. WINCHELL: So we understand that
4 physiologic dependence on nicotine is absolutely
5 biologically possible if not certain, and there are
6 some patients who will find that they are
7 physiologically dependent on nicotine and that it is
8 sufficiently uncomfortable for them to try to
9 discontinue use; that they'd rather continue using NRT.
10 As we said, we don't think that is a terrible thing.

11 On the other hand, there are some
12 patients -- and this speaks to the confusion in the
13 nomenclature between dependence, and addiction, and any
14 other language that may be invoked. There are people
15 who articulate a sense of being hooked on or unable to
16 control their use of nicotine replacement products.
17 You know, they're preoccupied with obtaining a supply.
18 They use it at times when it's not convenient, or they
19 wake up in the middle of the night and use it.

20 Certainly, we see that with
21 nicotine-containing products, and once in a while,
22 you'll see a patient describe that. So I think we

1 would probably think that that was an adverse event of
2 concern, whereas a patient who -- there is very little
3 reason, actually, to imagine that a person would call
4 up and report to the company, "I quit smoking, but I'm
5 sort of happily sporadically using Nicorette Gum." It
6 doesn't seem like an adverse event.

7 DR. NEILL: Thank you.

8 So I've gone through the list, and Dr. Parker,
9 I do have you on the list. However, Dr. Krinsky, who's
10 not yet asked a question, I think has one. And with
11 your permission, we'll go to him first to broaden the
12 scope of questions, and then come back to you. Any
13 others of you who have clarifying questions for FDA,
14 please make sure to get Dr. Chee or my attention, and
15 we'll make sure that you're addressed.

16 Dr. Krinsky?

17 DR. KRINSKY: Thank you. Dan Krinsky. In the
18 FDA briefing document on page 39, there's a comment
19 about how the users of the nicotine mouth spray were
20 asked to track their use with a hand-held counter. Was
21 there any assessment on how adherent they were to using
22 that counter in relation to the data reported, and then

1 how practical that type of tracking system might be in
2 the real world? Thank you.

3 DR. WINCHELL: I might throw that back to GSK.
4 I don't believe we were given any specific information
5 about the counter. We were given usage information
6 that was reported by the -- the use of the counter to
7 support that reporting of their use of the product
8 wasn't specifically addressed.

9 DR. NEILL: So sponsor, if you don't mind,
10 this is now a third set of data, that if you'd be so
11 kind as to think about and collect, we'll ask you to
12 address that later as well.

13 Is that okay, Dr. Krinsky?

14 (Dr. Krinsky gestures yes.)

15 DR. NEILL: Great. Dr. Parker?

16 DR. PARKER: So one question I had is what
17 happens when nicotine gets in your eye since that was
18 one of the label comprehension issues that came up.
19 What do we know about that? I have one other after
20 that. It was felt to be a primary endpoint in the
21 label comprehension.

22 DR. KELTY: Yes. We felt that that was a

1 significant safety concern because of the potential for
2 irritation in the eye. We don't know of any serious
3 adverse events that have occurred with application of
4 this into the eye or exposure into the eye, but that
5 being a different intended area of exposure, we thought
6 that was something important to test on the label.

7 DR. MICHELE: I'll just also note --

8 DR. NEILL: Dr. Michele?

9 DR. MICHELE: Thank you. Terri Michele, FDA.
10 I'll just also note that we often test whether people
11 understand where they should be spraying a spray device
12 because I am constantly amazed at how frequently folks
13 get it wrong.

14 DR. NEILL: Thanks for putting that picture in
15 our head.

16 (Laughter.)

17 DR. NEILL: Dr. Pruchnicki? I'm sorry.

18 Dr. Parker, do you have a follow-up?

19 DR. PARKER: Just one other quick question,
20 and that was I understand and appreciate the work that
21 the agency's done to try to look at what we know and
22 don't know, which are very different, I think, about

1 long-term exposure to nicotine. And my question is,
2 could you speak specifically to what we do or don't
3 know about long-term exposure that begins.

4 Even though this product's intended for 18 and
5 older, if it went over the counter, the whole thing of
6 age selection is an issue in some of these. We talked
7 about the availability in other countries of this
8 spray, even in a younger age. But what about long-term
9 nicotine exposure that begins in someone who's 11 or
10 12, who might somehow get a hold of it because they
11 have nicotine addiction, and they're trying to figure
12 out how they might come off of that?

13 So what do we know about long-term exposure to
14 nicotine that begins in a younger person and the impact
15 of that, and how it might compare to that of an adult?

16 DR. WINCHELL: Celia Winchell. I'm going to
17 say that in the evaluation of the risks and benefits of
18 all of these nicotine replacement products, we have
19 made the assumption that the patient or the consumer is
20 already exposed to nicotine. These products are
21 intended for people who are smoking cigarettes.

22 So whatever the harm might be of nicotine

1 exposure, we posited that that consumer is already
2 experiencing that harm and taking that risk, and that
3 these nicotine replacement products we understand may
4 also carry the risk of nicotine, but they clearly carry
5 fewer risks than continuing smoke.

6 So I am sure that there's information about
7 the developmental effects of nicotine on the adolescent
8 brain, and it can't possibly be good. But for the NRT
9 products, we consider that folks are already exposed to
10 nicotine.

11 DR. NEILL: Thank you. Dr. Pruchnicki?

12 DR. PRUCHNICKI: Maria Pruchnicki. It was
13 referenced earlier that with the current
14 over-the-counter products for nicotine replacement,
15 that they're generally unpalatable, and we don't worry
16 very much about minors using them because of that sort
17 of perception or reality if they have tried them.

18 Do we have any idea, with the nicotine spray,
19 how long some of the side effects might last, such as
20 throat irritation, or pharyngeal pain, and can it be
21 attenuated by drinking something or flushing the mouth.
22 Do we have any of that information? Are they equally

1 unpalatable for as long?

2 DR. NEILL: So I'm going to invite FDA, since
3 this is clarifying questions for you, if you have
4 anything from data. And if not, this is now a fourth
5 piece of data we're looking for from the sponsor.

6 DR. MICHELE: We don't have any specific data
7 to that point, and we defer to GSK.

8 DR. NEILL: Thank you. Dr. Farber?

9 DR. FARBER: Neil Farber, UC San Diego. So
10 going back to the issue of the spray being an adverse
11 event, spraying in the eye, I would wonder if there are
12 any data available in patients who have glaucoma, for
13 example, or other eye diseases where it actually might
14 make a difference rather than just an irritation.

15 DR. MICHELE: So again, we don't have that
16 data. We defer to GSK.

17 DR. NEILL: Now a fifth piece of data that
18 we're looking for. I have nobody else on the list of
19 clarifying questions for FDA. It is still a few
20 minutes before noon. By way of process, what I'd like
21 to propose is if sponsor is ready with some of the data
22 from Dr. Parker's earlier question, perhaps we could go

1 to that.

2 Because we still have some clarifying
3 questions on the list that have not yet been asked and
4 we are stacking up data, I will share that when we
5 return from lunch at 1:00, we have an open public
6 hearing that will occur at 1:00.

7 Depending on the duration of that open public
8 hearing, if time permits, we will ask sponsor to
9 present data to close the end of the questions that
10 have been asked in FDA clarifying question time. If we
11 don't have time, then we will finish with clarifying
12 questions both for sponsor and for FDA before we begin
13 to address questions to the committee this afternoon.

14 DR. MISHRA: Thank you. We have Julie Aker.
15 I think she'll be able to address some of the labeling
16 related questions that Dr. Parker had.

17 DR. NEILL: Julie, while you're coming to the
18 podium, Ruth, I can't remember your earlier question.
19 Do you? And if so, could you repeat it?

20 DR. PARKER: So my earlier questions were to
21 see the actual product, and the label, and the
22 packaging, and the user guide for us to be able to

1 actually see it, hold it, and look at it. I wanted to
2 know the size of the font on it. I wanted to know
3 about the six label comprehension questions that we
4 never heard about, and I wanted to know how the
5 question that related to inhalation was actually asked
6 to get a sense of how label --

7 DR. NEILL: I see. Let's see how many of
8 those we can get through in the next five minutes.
9 Thank you.

10 MS. AKER: So the first one, if I can do them
11 in a slightly different order here, is RR-4. Ruth,
12 these were the six questions that you asked about.
13 These were more profiling questions about the
14 population. The first one was how many cigarettes do
15 you smoke daily? We were just trying to characterize
16 the population here, so you see that there's a
17 distribution here of the different amounts, whether
18 they were a heavy or light smoker, and there was a
19 spectrum here.

20 The second question, question 20, was about
21 have you attempted to quit smoking in the past; yes or
22 no? And you'll note that quite a number of people,

1 80 percent, said that they had tried to smoke in the
2 past.

3 The next question was question 21. How many
4 times have you attempted to quit smoking? And you see
5 there was a spectrum there, but also it's weighted
6 towards 2 or more times. And if they said yes at
7 question 20, then we asked them how they've tried to
8 quit smoking. So you can see what the questions were
9 there, or the responses. Many of them tried to quit
10 cold turkey, and then they've used a variety of other
11 methods as well.

12 Our sixth goes on to ask the next question,
13 which is if open -- this was about the DFL flap that we
14 talked about earlier, and we're happy to address
15 further questions about the flap. That is a
16 fundamental behavior that we see in all studies, and I
17 will tell you that it's even more of an issue when we
18 do testing in Canada because if you are not aware of
19 it, now they've changed some of the rules in Canada
20 where they have to put both French and English on the
21 exterior, which is making all of those labels -- many
22 of them have to have peel backs, and they're becoming

1 quite extensive.

2 So this behavior of not wanting to break the
3 package or being afraid that they're going to do
4 something wrong is pretty typical. And I will say that
5 we actually did do an analysis here, and less than
6 5 percent of the population in this study, in that
7 label comprehension study, actually said that they
8 didn't see the warning or the indication to lift, only
9 less than 5 percent.

10 These remaining two questions here were about
11 opening the flap, and you can see that most of them
12 said that they did see it. They knew what it meant.
13 It meant to get more information and so forth. And
14 then the last question was there was a group of
15 individuals that asked permission.

16 Some individuals opened it straight away; some
17 individuals asked permission may I open it, and that's
18 what this last question relates to. "Why did you ask
19 permission? You asked to open it. Did you not see it?
20 What was the reasoning there?" And you can see what
21 their rationale was.

22 Does that address your questions, Dr. Parker?

1 DR. PARKER: So on the first slide, none of
2 those relate to what's actually on the label. They're
3 just like background, but they're called label
4 comprehension questions. They're part of the analysis
5 of the 18 even though they had nothing to do with what
6 was on the label.

7 MS. AKER: This was just profiling the
8 population.

9 DR. PARKER: And there's one more.

10 MS. AKER: One, two, three, four, five, six.
11 I've got six.

12 DR. PARKER: I must have missed one on the
13 first slide.

14 MS. AKER: The first slide had three, the
15 second slide had one, and then we've got this, these
16 two.

17 DR. PARKER: That's five, but that's okay.

18 MS. AKER: I've got three in the first page.

19 DR. PARKER: This is five, and there's one
20 more.

21 MS. AKER: Oh, I'm sorry. Slide 5. I
22 apologize. Slide 5, what methods have you used to quit

1 and passed? And slide 6 up? Did you get to see them
2 all, Dr. Parker?

3 (Dr. Parker gestures yes.)

4 MS. AKER: Okay. The next question related to
5 font size. This RR-7. Slide up. So we annotated this
6 for you. This is the picture that I showed earlier, so
7 you can see -- I won't read those all out to you, but
8 you can scan down through what the font sizes are in
9 the various areas.

10 DR. PARKER: So am I right that the active
11 ingredient that says that this is nicotine, is it a 6
12 to 8-point font? Am I reading that correctly?

13 MS. AKER: Yes. As I interpret this, header
14 there, active ingredient, is 8 font, and the one below
15 is 6-point font. And this is aligned to a 1.66 in the
16 Code of Federal Regulations for the drug facts label.

17 DR. NEILL: I realize we haven't gone through
18 all of your questions, but I'm just impressed that they
19 have a rapid Ruth response.

20 (Laughter.)

21 DR. NEILL: And having known you for as many
22 years as I have, it's not surprising to me at all.

1 We will now break for lunch. We will
2 reconvene again in this room in one hour from now at
3 1:00 p.m. Please take any personal belongings you may
4 want with you at this time. Committee members, please
5 remember that there should be no discussion of the
6 meeting during lunch amongst yourselves, with the
7 press, or with any member of the audience. Thank you.

8 (Whereupon, at 12:01 p.m., a lunch recess was
9 taken.)

10
11
12
13
14
15
16
17
18
19
20
21
22

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

(1:00 p.m.)

Open Public Hearing

DR. NEILL: Good afternoon.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, it's direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not

1 have any such financial relationships. If you choose
2 not to address this issue of financial relationships at
3 the beginning of your statement, it will not preclude
4 you from speaking.

5 The FDA and this committee place great
6 importance in the open public hearing process. The
7 insights and comments provided can help the agency and
8 this committee in their consideration of the issues
9 before them.

10 That said, in many instances and for many
11 topics, there will be a variety of opinions. One of
12 our goals today is for this open public hearing to be
13 conducted in a fair and open way where every
14 participant is listened to carefully and treated with
15 dignity, courtesy, and respect. Therefore, only speak
16 when recognized by the chairperson. Thank you for your
17 cooperation.

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

22 MR. HENIGAN: Thank you, Mr. Chairman. My

1 name is Dennis Henigan. I'm vice president for legal
2 and regulatory affairs at the Campaign for Tobacco-Free
3 Kids. I'd like to thank the committee for the
4 opportunity to speak with you today, and I want to
5 refer the committee to the written comments that we
6 filed before the committee earlier this month.

7 I will not be addressing the data submitted by
8 GSK in support of its new drug application, nor will I
9 be addressing the merits of the application itself.
10 Instead, I want to talk more generally about the need
11 for a new approach by FDA to the evaluation of drug
12 therapies for smoking cessation.

13 I think it's important for any advisory
14 committee, addressing an issue involving smoking
15 cessation, to understand that the public health
16 community and many experts in this field have long
17 urged FDA to more aggressively support the development
18 of innovative therapies.

19 I want to briefly review the history of those
20 efforts and FDA's response, and I think it will be
21 clear that there remains a need for a new agency
22 approach to these medicines. Indeed, I think the need

1 for change is more dramatic now than ever, and I'll
2 explain why in a moment.

3 Before I go further, I want to say in the
4 interest of full disclosure that the Campaign for
5 Tobacco-Free Kids receives about 1 percent of its
6 funding from corporate sources, and those include CVS,
7 GSK, and Pfizer. So let me begin by briefly discussing
8 the dimensions of the smoking problem and its
9 extraordinary implications for public health.

10 According to the Centers for Disease Control,
11 smoking is the leading cause of preventable deaths in
12 this country. It claims over 480,000 lives every year,
13 and to put that in perspective, that is more than the
14 number killed by AIDS, alcohol, motor vehicles,
15 homicides, illegal drugs, and suicide combined.

16 More than 16 million Americans suffer from
17 debilitating smoking-related illnesses, and despite
18 great progress in recent years in reducing smoking
19 prevalence among young people and adults, about
20 34 million Americans still smoke, and one half of
21 long-term smokers will lose their lives because of
22 smoking-related illnesses.

1 Now, as you've heard earlier, most smokers
2 want to quit, but quitting is terribly difficult
3 because of the effect of nicotine, one of the most
4 addictive drugs known to man. You heard the
5 statistics; 68 percent of smokers want to quit;
6 55 percent make a quit attempt in a given year; only
7 7.4 percent are successful, and of those who make a
8 quit attempt, only one-third even use an FDA-approved
9 medication. Even when these approved medications are
10 used, the quit rates are less than optimal, relatively
11 low from 17 percent to about 33 percent. So smokers
12 want to quit, but current medicines are simply not
13 giving them the help they need.

14 The need for innovation in this area is clear.
15 Most of the existing NRTs were developed and approved
16 over 20 years ago. As to non-nicotine products, no new
17 medications have been approved for the last 10 years.
18 So for a full decade, there has been little development
19 and approval of new smoking cessation products. The
20 public health community has repeatedly called on FDA to
21 seriously reassess its approach to smoking cessation
22 products, yet, other than modest changes in labeling

1 that were made in 2013, little has been done.

2 Now, more recently, there have been
3 encouraging signs from FDA's leadership that recognizes
4 the need for a new approach. In July of 2017, then
5 Commissioner Gottlieb announced a new comprehensive
6 approach to nicotine regulation in which he challenged
7 the agency to address the performance of medicinal
8 nicotine products. He created a new agency-wide
9 nicotine steering committee to address the need for
10 innovation.

11 The committee convened a public meeting in
12 January of 2018, where it heard testimony from academic
13 experts, pharmaceutical companies, public health
14 groups, suggesting concrete steps towards change. And
15 although CDER has issued two draft guidances on NRT
16 since that meeting, neither has been made final, and in
17 our view, neither proposes the kinds of reforms that
18 are urgently needed.

19 So let me give you some idea of concrete ideas
20 for change in FDA's approach that have been advanced by
21 the public health community. First, in evaluating the
22 risks of new indications, or labeling changes for

1 existing products, or the risks of potential new
2 products, FDA must compare those risks to the risks
3 posed by continued smoking.

4 FDA regularly assesses product safety and risk
5 in the full context of the condition for which the
6 product is to be used, and cigarettes, as I said, kill
7 half of their long-term users. In evaluating the risks
8 of smoking cessation products, the acute lethality of
9 cigarette smoking must be the relevant comparator.

10 Second, labeling changes where existing
11 approved products could be made to support new
12 innovative treatment regimens. Some examples include
13 combination use of approved products, longer term use
14 of NRTs, and pre-quit use of NRTs in a reduced to quit
15 regimen. The current labeling does not sufficiently
16 support the effectiveness of any of those uses, even
17 though they are supported by substantial science.

18 Third, FDA should fully explore possible
19 regulatory changes to create a regulatory environment
20 that encourages the development of new innovative
21 products, particularly to reduce the time and expense
22 of the approval process. For example, for particularly

1 promising new products and indications, and without
2 weakening agency standards for safety and efficacy, FDA
3 should explore broadening the kind and scope of
4 scientific evidence beyond long-term clinical trials.
5 This effort should recognize that there is already a
6 wealth of data from multiple sources across the globe
7 about the delivery of nicotine.

8 FDA should also lay the groundwork for the use
9 of accelerated pathways to approval like fast track
10 treatment or designation as breakthrough therapies for
11 promising products. And finally, any effort by FDA
12 through CDER to create a new regulatory environment for
13 the development of smoking cessation products must be
14 closely coordinated with FDA's Center for Tobacco
15 Products.

16 I noted at the outset that the need for change
17 in this area is now more urgent than ever. Why is this
18 so? Because now we have the emergence of the exploding
19 largely unregulated market for e-cigarettes in which
20 millions of Americans are using these products,
21 believing they will help them quit smoking. They are
22 being advertised in full-page ads as smoking cessation

1 AIDS, yet no company has been required to prove that
2 their products are safe and effective for that
3 therapeutic purpose. And as we have seen, the
4 unregulated marketing of e-cigarettes has caused an
5 epidemic of youth usage of these highly addictive
6 products in which now 1 in 4 high school students is a
7 current user. As a father of a 14 year old, I find
8 that appalling and very scary.

9 We now have hundreds of recent cases of acute
10 respiratory illnesses associated with these products,
11 including, now as of today, 7 reported deaths
12 associated with e-cigarette use. A root cause of the
13 current e-cigarette crisis is that current FDA
14 regulation across the agency creates perverse
15 incentives.

16 Responsible companies have little incentive to
17 develop safe and effective medicinal nicotine
18 therapies, while irresponsible companies are rewarded
19 for marketing nicotine products to kids and making
20 unsubstantiated drug claims aimed at smokers, who are
21 then driven to use these unproven products because the
22 FDA-approved treatments have proven inadequate. So a

1 new approach by CDER to cessation medicines must be
2 coordinated with a serious effort by CTP to bring the
3 wild, wild west of e-cigarettes under control.

4 Now, FDA last week took a significant step in
5 the right direction by moving to clear the market of
6 flavored e-cigarettes so appealing to young people, but
7 CDER and CTP must work together to change this
8 incentive structure to enable the right products, but
9 only the right products, to reach the market; products
10 that actually help smokers quit without threatening to
11 hook yet another generation of our kids on nicotine.

12 DR. NEILL: Thank you, Mr. Henigan.

13 Will speaker number 2 step to the podium and
14 introduce yourself? Please state your name and any
15 organization you are representing for the record.

16 DR. SPANGLER: Good afternoon. I'm David
17 Spangler. I'm with the Consumer Healthcare Products
18 Association. We represent over 60 manufacturers of OTC
19 medicines, including OTC nicotine replacement therapy
20 and including GlaxoSmithKline and Johnson & Johnson. I
21 want to very quickly cover four areas.

22 First, we all know that helping people quit

1 smoking and stop tobacco product extends use, extends
2 lives. We also know that's not easy. Nicotine is
3 addictive; that is that typically the use is chronic;
4 there's frequent relapse by those seeking to quit; it's
5 frequently characterized by compulsive seeking of
6 nicotine; and, too often, continued use despite harmful
7 consequences.

8 As the National Institute of Drug Abuse notes,
9 for many tobacco users, long-term nicotine exposure
10 frequently involves withdrawal symptoms when not
11 smoking. Most smokers, CDC's National Health Interview
12 Survey shows over two-thirds would like to stop
13 smoking. In a given year, CDC's surveys show roughly
14 half of smokers make a quit attempt in a given year.
15 Yet, these same CDC surveys find only about 6 to
16 8 percent of smokers are able to quit in a given year.
17 In other words, quitting is a journey, and it can be a
18 complex one.

19 The complexity of the journey to quit leads to
20 my second point, the importance of choice. Smokers, or
21 more broadly, tobacco users, aren't all the same. The
22 path to quit could be shorter, could be longer, and as

1 I said a moment ago, it usually takes multiple
2 attempts. And multiple attempts suggest how critical
3 multiple options to help a smoker on their path to
4 quitting can be. As NIH, FDA, and CDC have said
5 repeatedly, every try counts. Whether it be
6 individual, group, or telephone counseling, or existing
7 FDA-approved medications, more tools help more people
8 quit.

9 I have to personally believe that adding a
10 medication to this picture will help more people on
11 that journey. And I say that not solely about smoking,
12 quitting smoking, but because we know more choice can
13 lead to greater utilization. Among those choices could
14 be different consumer preferences among dosage forms,
15 in flavors, in packaging configurations, or other
16 differences among the options available.

17 Let me provide an example totally unrelated to
18 nicotine. Let's look at allergies. When Americans
19 were given more OTC medicine options to address their
20 allergy symptoms, the results were that more Americans
21 utilized these options. Allergy sufferers using OTC
22 medicines went from 66 percent in 2009 to 75 percent in

1 2015. This was a time period of the last switch in a
2 series of three non-sedating antihistamines and the
3 introduction, OTC introduction, of allergy relief
4 sprays. More choices, including different dosage
5 forms, was followed by greater utilization.

6 Back to nicotine replacement therapy
7 specifically, history suggests this is precisely what
8 happens here as well. Giving people the direct OTC
9 access to the very first NRT products led to a 150
10 percent increase in their use in the first year after
11 expanding access, expanding choice, in turn leading to
12 hundreds of thousands of new former smokers annually.

13 Given our government's existing Every Try
14 Counts campaign that highlights NRT's role in dealing
15 with cravings, and the fact that it can double a
16 person's chances of quitting, yes, I think more options
17 means more help. The headlines of the last few weeks
18 only serve to underscore the importance of helping more
19 people in their journey to break nicotine addiction.

20 Fourth and last, I'm well aware that it is not
21 FDA's role to base its decisions on economic
22 considerations, but one way we societally measure

1 benefit is to translate it into measurable economic
2 terms. Let's look at a quick model specific to NRT
3 based on a larger study that CHPA released with the
4 data analytics and retail purchase tracking firm IRI.

5 5.2 million Americans used OTC NRT last year.
6 If we take the lowest end, not the mid, not the high,
7 the very lowest end of CDC's estimated successful quit
8 percentage, that translates to 286,000 quitters. If we
9 next look at a conservative one-year direct medical
10 expenditure figure that's attributable to smokers,
11 that's about 4,600 a year, per person/per year. That's
12 direct and annual. That's not including indirect.
13 That's not including longer-term impacts.

14 The product of those last two figures gets us
15 to 1.3 billion in annual direct medical care savings
16 from OTC NRT. With more aggressive quit rate
17 estimates, that figure of course gets larger. So where
18 does that leave us? Most tobacco users want to quit.
19 Quitting is a journey, and more tools and more choice
20 means more help to more Americans in their journey.

21 DR. NEILL: Thank you.

22 Will speaker number 3 step to the podium and

1 introduce yourself? Please state your name and any
2 organization you are representing for the record.

3 MS. SWARD: Good afternoon. My name is Erika
4 Sward, and I am the national assistant vice president
5 for advocacy at the American Lung Association. The
6 Lung Association receives our funding primarily from
7 individual donors, foundations, federal, state, and
8 local governments. We also do receive funding from
9 CVS, GSK. and Pfizer.

10 The American Lung Association works on behalf
11 of the 35 million Americans living with lung diseases,
12 including lung cancer and COPD, which are primarily
13 caused by tobacco use and exposure to second-hand
14 smoke. Tobacco use remains the leading cause of
15 preventable death in the United States, killing 480,000
16 Americans every year. Another 16 million Americans
17 live with a tobacco-caused disease.

18 The American Lung Association does not take
19 positions on whether a pending application for a new
20 tobacco cessation therapy should be approved or denied;
21 instead, I am here to urge FDA, and CDER especially, to
22 do more to promote and support the development of

1 products that are safe and effective in helping all
2 tobacco users and their addiction for good.

3 As was mentioned earlier, FDA has not approved
4 any new tobacco cessation treatments in 10 years, and
5 most of the current NRTs were approved more than 20
6 years ago before we saw the explosion in e-cigarette
7 use. Innovation and safe and effective cessation
8 therapies has been all but dormant.

9 In April, the American Lung Association and
10 our partners submitted comments to the FDA in response
11 to FDA's draft guidance, Smoking Cessation and Related
12 Indications: Developing Nicotine Replacement Therapy
13 Drug Products, Guidance for Industry, urging the FDA to
14 address the barriers and innovation in smoking
15 cessation products and to adopt measures that would
16 encourage more widespread use of NRTs that are proven
17 safe and effective to help people quit cigarette
18 smoking.

19 Approximately 70 percent of smokers say they
20 want to quit, but it's an incredibly powerful
21 addiction. The Lung Association believes that a
22 significant portion of the remaining 30 percent of

1 smokers who say they don't want to quit would still
2 like to do so, but they're feeling defeated and worried
3 that they will fail at quitting. And of course there's
4 a good likelihood they will fail at quitting along the
5 way before ultimately being successful. It takes an
6 average of 8 or more quit attempts for most smokers to
7 end their addictions for good.

8 One of the American Lung Association's core
9 beliefs is that every smoker can quit using all tobacco
10 products. The Lung Association does not accept the
11 idea that a certain percentage of tobacco users can't
12 quit; only that access to those evidence-based and
13 proven effective treatments, including a combination of
14 behavioral modification counseling plus
15 pharmacotherapy, have not reached these underserved
16 individuals. We recognize that smokers must be met
17 where they are and that no one size fits all will work
18 for helping them in their addiction.

19 According to data released by FDA and the CDC
20 last week, there are now 5 million kids who are using
21 and likely addicted to e-cigarettes. There are also
22 millions of Americans who are addicted to cigars and

1 cigarettes, including menthol cigarettes. Given how
2 the tobacco industry is currently addicting youth and
3 young adults on these products, there's an urgent need
4 to help them end their addiction to nicotine and to
5 tobacco products for good.

6 FDA must also crack down and stop therapeutic
7 claims being made by e-cigarette manufacturers. No
8 e-cigarette has demonstrated its safety and efficacy.
9 FDA has not approved any cigarette for smoking
10 cessation; still, many companies are making therapeutic
11 quit smoking claims.

12 The public wants and needs safe and effective
13 tobacco cessation therapies. The American Lung
14 Association respectfully urges CDER to incentivize and
15 prioritize innovations and therapies that can meet
16 standards for safety and efficacy so that we can
17 eliminate tobacco use and tobacco-related diseases.
18 Thank you for your time.

19 DR. NEILL: Thank you.

20 Will speaker number 4 step up to the podium
21 and introduce yourself? Please state your name and any
22 organization you're representing for the record.

1 MS. ZELDES: Good afternoon. My name is Nina
2 Zeldes, and I am a senior fellow at the National Center
3 for Health Research. Our research center analyzes
4 scientific and medical data and provides objective
5 health information to patients, providers, and
6 policymakers. We do not accept funding from drug and
7 medical device companies, so I have no conflicts of
8 interest. Thank you for the opportunity to share our
9 views.

10 As a colleague of the Campaign for
11 Tobacco-Free Kids and partners for effective tobacco
12 policy, we of course agree with other members of the
13 coalition that effective smoking cessation treatments
14 are needed. However, to our knowledge, we're the only
15 member of the coalition that has analyzed the data for
16 this specific product, and as a result of our analysis,
17 we are very concerned about its safety and efficacy.

18 This nicotine mouth spray has already been
19 approved in several other countries, but that doesn't
20 mean that it's a good product for the U.S. We already
21 have a major problem with addiction from nicotine
22 delivery systems such as e-cigarettes, especially among

1 teens, and if you've learned anything from the JUUL and
2 vaping epidemic, it is that anything that delivers
3 nicotine over the counter or online can be abused.

4 Making this product available in the U.S.,
5 especially over the counter, is obviously of concern.
6 It is important that we do not assume that any nicotine
7 product to be safe and effective for smoking cessation
8 unless there's evidence, clear evidence,
9 it is. Only one study examined the efficacy of this
10 treatment in an over-the-counter setting. Only
11 3.4 percent of participants using this nicotine mouth
12 spray continued to not smoke at the end of the study
13 compared to 1.2 using the placebo. This 2.2 percent
14 difference is not clinically meaningful. The rest
15 continued to smoke and 79 percent smoked while also
16 using this cessation product.

17 The risks of this ineffective treatment
18 include dependence, misuse, or abuse and other adverse
19 events. Cases have been documented in the postmarket
20 adverse events reporting systems, and because these are
21 voluntary reporting systems, they underestimate the
22 actual incidence. The reported difficulties with

1 locking, unlocking, and priming may also increase the
2 risk for accidental exposures to non-users.

3 Additionally, this product is similar to
4 e-cigarettes, and it is easy for people to lose track
5 of how much they have consumed until the container is
6 empty. This may lead to people ingesting much more
7 nicotine than intended or than is safe. The labeled
8 comprehension study also raised concerns that
9 participants did not understand or were not aware of
10 the label. This reduces the likelihood that the
11 product will be used safely.

12 There already are FDA-approved nicotine
13 replacement products available both over the counter
14 and by prescription. All seem to be more effective
15 than this new product. A new treatment, particularly
16 one that could increase addiction to nicotine, should
17 not be approved unless it has demonstrated proven
18 benefits that outweigh the risks. This product does
19 not. Thank you for your time.

20 **Clarifying Questions (continued)**

21 DR. NEILL: Thank you.

22 It's now 1:26. The open public hearing

1 portion of this meeting has now concluded, and we will
2 no longer take comments from the audience. Because we
3 have a bit of time, I'd like to revisit now clarifying
4 questions to sponsor, and begin with the remainder of
5 Dr. Parker's questions. I think sponsor has devices
6 that can be shown to the committee. Once we've gone
7 through that additional data, I also still have four
8 questions from earlier this morning that were never
9 asked of sponsor.

10 I'm going to ask Dr. Curry, Hatsukami, and
11 Di Francesco if you still recall those clarifying
12 questions, we will get to those.

13 Sponsor, do you have those devices?

14 MS. JAMES: Yes. Thank you, Dr. Neill. Can
15 we have your permission to approach the committee to
16 pass out some samples, please?

17 DR. NEILL: Why, yes. Thank you for asking.

18 (Laughter.)

19 (Samples distributed to committee.)

20 MS. JAMES: We have prepared some samples for
21 the committee, which will be handed out. When you have
22 these samples in your hand, what you will be looking at

1 is the culmination of our learning since our study 38
2 and the associated labeling that was in our briefing
3 book appendix, 11.1 and 2. We have enhanced the
4 materials to assist consumers in their ability to quit
5 and use the product.

6 The samples that we all handing out are the
7 actual proposed labeling. You may use the product,
8 take it to pieces, and do the reading. There all some
9 elements of this product that are not consistent with
10 what we would plan to commercialize. Just quickly,
11 this open peel strip on the top, this will be a tamper-
12 evident feature for marketed product. It will shred
13 when you peel it to make it obvious to any consumer who
14 purchases that it has been tampered with prior to
15 purchase.

16 The label at the back has got one little blob
17 of sticky. That will be a little more robust,
18 actually, on commercial product for shipping purposes.
19 The user guide is on the inside -- maybe it will be
20 less noisy to -- the user guide on the inside is the
21 proposed user guide, and the canister that we have here
22 is the proposed canister. However, this has been

1 manufactured or we put it together with placebo
2 product. So you are more than welcome to spray it. It
3 is placebo product. To Dr. Michele's point, please
4 make sure the spray is pointing towards your tissue.

5 Now, on our website to help consumers use
6 these products effectively, we will have a video, and I
7 would ask that we can play that, which means I need to
8 ask audio to please turn the volume up, if we can play
9 that to demonstrate how we recommend the product be
10 used.

11 (Video played.)

12 MS. JAMES: Thank you. Please feel free to
13 hold on to those samples for the rest of the day. We
14 will need to collect them at the end of the meeting.
15 Thank you. I will now turn over to Raj Mishra again to
16 moderate the questions.

17 DR. NEILL: Thank you. I just want to
18 reiterate, these will be collected at the end.

19 DR. MISHRA: Thank you. Raj Mishra, Johnson &
20 Johnson. We'll begin with bringing Julie Aker back to
21 address some of the outstanding questions from Dr.
22 Parker.

1 MS. AKER: I need RR-1, please. We have two
2 remaining questions. One was regarding, I believe on
3 this side of the table, about the human factors study
4 and the inclusion criteria.

5 Slide up. Slide 1 up. The question was asked
6 about what was asked in terms of the smokers from an
7 inclusion criteria. We simply asked if they were
8 currently smoking or trying to quit smoking. If they
9 were a self-reported smoker of any sort, we did say
10 cigarettes; are you smoking or trying to quit smoking
11 cigarettes? So we did not distinguish e-cigarettes.
12 We had one person in the study that mentioned that they
13 also smoked e-cigarettes.

14 I believe that was your question on this side
15 of the table. Did that address your question?

16 (Dr. Curry gestures yes.)

17 MS. AKER: The second question, RR-3, to
18 Dr. Parker. I believe you asked a question about the
19 question in the questionnaire that was asked related to
20 inhalation. This was question 13.

21 Slide up. The question was, according to the
22 label, is it okay or not okay to inhale while spraying

1 this product? Obviously, the pre-list at the bottom is
2 never shown. That's for the interviewer to score. So
3 they were just asked an open-ended question. After the
4 open-ended question, they had to give the rationale for
5 their response. That's the why do you say that
6 question afterwards.

7 DR. MISHRA: Thank you. Does that address the
8 questions so that we can move on to the next question?

9 One of the questions was around data on
10 persistent or dual use in lozenge trials. I'm going to
11 invite Dr. Nides, and I think he can reframe the
12 question as it was asked. And perhaps if the committee
13 member who asked the question wants to rephrase the
14 question, we'll be open to that.

15 Dr. Nides?

16 DR. NIDES: Mitchell Nides, Los Angeles
17 clinical trials. I think your question was around
18 other clinical trials, that it had a dual use, correct?

19 DR. FARBER: Right. Neil Farber, UC San
20 Diego. The question was regarding other clinical
21 trials for other products, besides lozenges, such as an
22 Nicorette Gum or patches, and the incidence of dual use

1 of continuing the nicotine replacement treatment as
2 opposed to also at the same time smoking.

3 DR. NIDES: In the short time we had, we did
4 the best we could. Partly, you have to go into the way
5 back machine to get some of these data. Let's look
6 first just at the clinical trial data for the nicotine
7 patch, RR-12.

8 Slide 2 up, please. These data are a little
9 bit dense in the way that they're presented, but this
10 is basically looking at a survival analysis of people
11 who on the active and 21-milligram patch, 14-milligram
12 patch, and placebo, how many were still abstinent as
13 time went on.

14 This is a 12-week trial, and you can see that
15 the majority of the people, as you continue to go
16 towards the end of the trial, are not abstinent, and
17 they're not asked to not use, to take the patch off
18 their arm. So they're all continuing to use, or not,
19 is there choice, to continue to use the product through
20 the full 12 weeks even if they're continuing to smoke.
21 And you don't see any increase in the adverse events
22 from those people who are using the product and dual

1 using versus those who are not. So this is typical of
2 an efficacy trial for an NRT.

3 Another example would be -- RR-11, please.
4 This is a trial, primarily a safety trial, looking at
5 adult smokers with heart disease, uncontrolled
6 hypertension, and/or diabetes randomized either to a
7 lozenge or gum. Again, this is open label, no placebo.
8 This is a 12-week trial. At the end of week 2,
9 91 percent were still smoking on the lozenge;
10 95 percent were still smoking using the gum. And even
11 when you got out to 12 weeks, still using 3 to 4 units
12 of the NRT, you saw no additional adverse events in
13 this at-risk population.

14 DR. MISHRA: I think there was another
15 question related to getting some more information on
16 the dose counters and studies, so if we could get some
17 more clarification around the exact kind of requests
18 there. Dr. Nides will come forward to address that,
19 understanding how the dose counter works.

20 DR. KRINSKY: Yes, that was me. I was just
21 curious as to what kind of data were collected from
22 those dose counters and how that compared patients that

1 abstained.

2 DR. MISHRA: Dr. Nides?

3 DR. NIDES: Mitchell Nides, Los Angeles
4 clinical trials. The counter was just like a clinical
5 trial diary, basically, to handle the subjects, to try
6 to keep track for what they were going to be putting
7 into the IVRS system that night. So it had no other
8 purpose except to collect those data to remind
9 themselves.

10 DR. MISHRA: There was a question around the
11 accidental exposure of the spray to the eye, obviously,
12 under normal conditions someone who sprayed it, and if
13 someone had maybe some glaucoma or some underlying
14 disease conditions. I'm going to invite Dr. Andrew
15 Myers from Johnson & Johnson to address that question.

16 DR. MYERS: Hi. I'm Andrew Myers from J&J.
17 In our safety database, we have had cases of reporting
18 exposure to the eye. In total, we have 116; 114 of
19 those are non-serious. They largely report stinging,
20 burning, and lacrimation. We have two serious cases.
21 One was considered serious because it actually reported
22 dependence. The ocular symptom itself was non-serious,

1 and the other case reported prolonged irritation or
2 stinging in a patient who had contacts and had no
3 structural eye outcomes. From a glaucoma point of
4 view, we are aware that smoking has been associated
5 with glaucoma. We have not had any reports of patients
6 with glaucoma spraying the product into their eye.

7 DR. MISHRA: Another question was around is
8 the canister itself -- what evidence or any information
9 we have seen from postmarketing and people trying to
10 get into this, tamper with this. Again, I'm going to
11 invite Dr. Andrew Myers to address the question around
12 any tamper efforts and what we have seen from our
13 postmarketing experience outside the U.S.

14 DR. MYERS: Thank you again. Andrew Myers,
15 J&J. We have had one postmarketing report of
16 tampering. That case came from the United Kingdom. It
17 was a patient reported that their 2-pack appeared to
18 have been tampered with. And when we followed up with
19 the reporter and the pharmacist, what we learned was
20 that the pharmacist had opened the double pack to sell
21 one, and had, I suppose, put that back on for resale.

22 DR. MISHRA: Thank you. The other question

1 was around when people experience oral irritation,
2 adverse events, such as mouth and throat irritation,
3 and hiccups, how does this progression evolve. And
4 also related to that was if people drink any fluids,
5 does that kind of go away or resolved?

6 From our experience, from the clinical trial,
7 as we've said in the core presentation, oral adverse
8 events are most common: hiccups, throat irritation.
9 Hiccups are quite predominant in the first week of the
10 trial. Slide 3 up, please. As you can see here,
11 almost 30 percent in the first week. Over the course
12 of 26 weeks in study 38, they had reduced about 3
13 percent, almost 33 percent in the start of the trial,
14 and then they were reduced.

15 So we see most of these events kind of
16 reducing their frequency. The mean duration of hiccups
17 is about a minute -- sorry, the median is about a
18 minute and the median is about 4 minutes. So most of
19 these are like self-resolving.

20 Another question is do fluids actually help?
21 I think because the mechanism of hiccup is like any
22 other oral irritant, if someone drinks some fluid, it

1 will obviously soothe that and help with the reduction
2 and any kind of oral irritation. Of course, as we
3 know, if you use any acidic drinks, acidic environment
4 will reduce the absorption of nicotine, so that's why
5 the label advises already in existing NRT products that
6 you should not idly drink any time before within 15
7 minutes of using the product.

8 I think that addresses the outstanding
9 questions. If you've missed anything, please remind
10 us, but I think we've covered all the six questions,
11 including the one which was from Dr. Parker. We can go
12 to the other questions, then.

13 DR. NEILL: Thank you. So I have Dr. Curry,
14 both an asked question from this morning, and I think
15 you may have had a follow-up regarding the counter or
16 dose. But we're going to go to you first, then
17 Dr. Hatsukami, Dr. Di Francesco, and I have a question
18 as well. Dr. Curry?

19 DR. CURRY: Thanks. These questions are asked
20 in the context of vaping, which wasn't a context I
21 think when this technology was originally developed.
22 They relate to inhalation used by youth. I noticed

1 that when we asked a question about inhalation, one of
2 the answers was if someone were to try to inhale this,
3 they would probably get the hiccups. I'm paraphrasing,
4 but hiccups came out pretty clearly.

5 Nearly half of the people who -- we have
6 adverse -- and it's considered a non-serious adverse
7 event as a hiccup, but it just got me wondering about
8 whether that's an indicator that a lot of people are
9 trying to inhale this. Then if the hiccups go away
10 over time, is that in any way equivalent to my own
11 experience, when I started smoking, of having some
12 pretty adverse events, and the longer I exposed myself
13 to it, the less adverse it became.

14 So that's one thing I think that we need to
15 have a conversation about. Then the other is use by
16 youth. Obviously, the indication for this is age 18
17 and over. That's also the indication for being able to
18 buy e-cigarettes, and yet we have an epidemic of youth
19 use. Being able to get those I think is sometimes
20 attributed to being able to buy them on the internet.
21 And when I did a quick search, you can buy nicotine gum
22 and other products on the internet, and I could have it

1 delivered to my house by this afternoon by Amazon.

2 So I'm just curious about plans for making
3 these things available over the internet. So those are
4 my two main questions.

5 DR. MISHRA: We'll start with the hiccups
6 question. I think I explained hiccups as one of those
7 symptoms, but if someone really tried to inhale this,
8 they will experience even other side effects, including
9 severe throat burning. They'll experience nausea and
10 vomiting.

11 So hiccups might be just one of the
12 parameters. But your question whether or not people
13 who were experiencing hiccups in the trial attempted to
14 inhale, we really don't have any specific data to
15 suggest one way or the other whether that was something
16 they attempted to do.

17 DR. CURRY: I just want to clarify that the
18 human factors study can't really answer that question.
19 And I guess part of the reason that I want to make sure
20 that we have this conversation is if a large proportion
21 of people, who've moved to this product, had been using
22 e-cigarettes, they're used to inhaling vapor. So to

1 what extent would that behavior -- I just sprayed it.
2 It smells like Vicks VapoRub; but to what extent might
3 that behavior follow?

4 If I look at the profile of non-serious
5 adverse events, I could -- and I'm not saying I would,
6 but I could construe that that's related to inadvertent
7 inhalation.

8 DR. MISHRA: One of the points we made earlier
9 also when the question was asked was the droplet size,
10 we've done testing with that. This is really much
11 larger droplets, 80 micrometer. Droplets are not
12 designed to really be in an aerosol form to enter the
13 lungs. If someone really desperately tried to do this,
14 even then, it's very highly unlikely that much of the
15 product would really go down the areas. Any attempt to
16 do this will cause severe oropharyngeal, I guess,
17 response, and it will make them feel unwell.

18 So we feel quite reassured from our data that
19 attempts to misuse in that way is not really going to
20 give people what the desired effect is, and they're
21 going to actually feel sick and stop using immediately.

22 DR. NEILL: Dr. Curry, you had a different

1 question about the internet, and Dr. Zorich, I can't
2 tell if you wanted to clarify this inhalation
3 discussion.

4 DR. ZORICH: I hate to do this, but I think
5 for the sake of just my own ability to continue to
6 follow, I think that young people go to these
7 e-cigarettes because they want to smoke, not because
8 they want to become addicted to nicotine.

9 Is that a false assumption? I mean, I see
10 people with these e-cigarettes, and it looks to me like
11 they're smoking. They're inhaling. They're exhaling.

12 DR. NEILL: I'm going to use the chair's
13 prerogative to define that as outside the purview of
14 sponsor or FDA. And despite being the parent of two
15 children myself, outside of my purview, my vote is
16 they're just trying to be cool.

17 DR. ZORICH: But this thing doesn't look cool.
18 I mean, that's a really good point. I just saw this.

19 DR. NEILL: And it's not Vicks VapoRub; it's
20 fresh mint.

21 (Laughter.)

22 DR. NEILL: Anyway, would you care to address

1 the internet marketing?

2 DR. MISHRA: Yes, the second question, and I
3 would like to invite Ken from GlaxoSmithKline to
4 address the e-commerce question.

5 MR. CHRISTENSEN: Hi. I'm Ken Christensen
6 from GSK. Thank you for the question. I think it's a
7 really important one. And I would make a couple of
8 points, potentially distinguishing our approach from
9 those of others who are pedaling nicotine products in
10 the marketplace.

11 If you were to look at our marketing, we are
12 squarely and exclusively focused on adult smokers who
13 are interested in quitting. We have a sophisticated
14 body of data that helps us to identify these people and
15 then reach them with our messaging. And our message
16 speaks exclusively about using the product to quit, not
17 for recreational purposes but to quit.

18 I think 15 years ago, if you were to take this
19 product and compare it to other therapies on the
20 market, it probably would have seemed sexy and
21 appealing to teenagers. I have a new teenager. I
22 think now arguably between the palatability of the

1 product, which is, we feel, just good enough to allow
2 people to sort of stomach it and get through the
3 therapy, and the look and feel of the product, it
4 really stands out so distinctly from the many other
5 products that kids unfortunately are using in the
6 marketplace.

7 But to address your question specifically
8 about e-commerce, because we are very concerned about
9 making sure that only the people whom we are targeting
10 are actually able to access the product, we work very
11 closely with our bricks and mortar retailers to ensure
12 that their cashier's check people's ID to make sure
13 that they are of age to buy the product.

14 But when it comes to our dot-com
15 partners -- and Amazon is the most significant at this
16 point -- we have pushed them to strengthen the
17 requirements they expect somebody to meet when they
18 purchase the product online. Right now their policy is
19 if you pay with a credit card, that's adequate
20 confirmation that you are at least 18 years or older.
21 We have not been able to get them to budge on that, but
22 they feel very strongly that that is an indicator that

1 the person is at least 18 years or older. So I hope
2 that answers your question.

3 DR. NEILL: Thank you. Dr. Hatsukami?

4 DR. HATSUKAMI: I have a couple of questions.

5 So my
6 understanding is when you did trial 38, you had a
7 user's guide that gave just some tips in terms of how
8 to quit smoking, but when you're going to actually
9 market this product, you're going to have quit.com
10 website that people can go to, and they can download
11 different programs. Some of them involve apps.

12 I guess my question is, what is the
13 utilization of that type of program with your other
14 products, the gum and the patch?

15 DR. MISHRA: Thank you. I would like Ken,
16 once again, to address that. Thank you.

17 MR. CHRISTENSEN: Ken Christensen from GSK.
18 Thank you for the question. Here it is. If we could
19 pull slide 1 up, please. We've worked tirelessly over
20 the last 20 years to develop a user friendly behavioral
21 support program that people will actually find easy to
22 embrace. And again, we've tried to put ourselves in

1 the shoes of people who are attempting to quit. It's
2 incredibly difficult. So if you put any barriers in
3 place to them adopting something like a behavioral
4 support program, they're not going to do it.

5 Are our tools perfect at this point? I'd say
6 no. There's always room for improvement, but we have a
7 pretty comprehensive suite of tools which we call
8 MyQuit, and the reason that we have multiple tools is
9 because, as the point was made earlier about choice
10 being important, we think that applies not just to the
11 product but also the delivery of behavioral support.

12 So as an example, recently we developed and
13 have now made available a mobile app that allows people
14 to get personalized quitting support on the go. They
15 go through a simple registration process where they
16 give us an idea of why they're quitting, how often they
17 smoke. We help them with product selection, and then
18 we provide tips and inspiration along the way.

19 The two more robust elements of the program
20 that have been around for a bit longer are quit.com,
21 which is a lightly branded, but frankly largely
22 unbranded website that contains a ton of content

1 designed to help people understand why it might make
2 sense for them to quit, what their options are, and how
3 they should expect to feel when they are quitting; to
4 reassure folks that it's going to be difficult, you're
5 going to stumble, but keep at it.

6 We heavily leverage testimonials from people
7 who have successfully quit. We have upwards of 70
8 videos of real quitters who speak about their personal
9 experience and try to provide encouragement to folks.
10 That website receives approximately a million visitors
11 annually.

12 Then the other major element of the program at
13 the moment is an email-based support program. We call
14 it the ECRM program, but it essentially allows somebody
15 to register for the program. Again, we collect some
16 basic information so that we can tailor the content to
17 their personal situation. And then they receive, over
18 the course of the 12-week quitting period, regular
19 emails that vary in content. Some are strictly meant
20 to inspire. It could be showing them a picture of what
21 they told us at the beginning was their reason for
22 quitting, a picture of their daughter, or a picture of

1 running outside, whatever is motivating to them.

2 But we also provide really rich content around
3 tips and guidance on how to get through challenges. We
4 allow them to provide feedback to us. We provide mini
5 rewards or badges along the way as a means of
6 recognizing the fact that they made it to day 2 or
7 week 2. And we've gotten some very compelling and
8 encouraging feedback from the users of that program
9 that it actually has made a tangible difference in
10 their ability to work their way through the therapy,
11 and ultimately to quit successfully. So I hope that's
12 helpful.

13 DR. ZORICH: Thank you.

14 DR. NEILL: Thank you. Dr. Di Francesco?

15 DR. DI FRANCESCO: Lorenzo Di Francesco at
16 Emory. I have a clarifying question about efficacy
17 study 38. CC-37 slide I guess would be helpful. I was
18 curious. Were all the individuals who were found to be
19 continuously abstinent the 6-week time point, were they
20 all tested at the 6-week time point? And if not, how
21 many of them were tested at the 8-week time point
22 because they missed the 6-week visit?

1 DR. MISHRA: Thank you. I'll invite Dr. Nides
2 to provide that clarification.

3 DR. NIDES: Mitchell Nides, Los Angeles
4 clinical trials. They were tested -- there was carbon
5 monoxide testing at every visit when they came into the
6 week 6 visit. So they had to come into the week 2
7 visit, week 4, week 6 visit, I believe in order to be
8 considered to meet the continuous abstinence
9 requirement. I don't think we had any who missed the
10 week 6 visit, came back at the week 8 visit, and then
11 were classified as a success at the week 6 visit if
12 that's what you're asking.

13 DR. DI FRANCESCO: That is what I was asking.
14 Thanks for clarifying.

15 DR. NEILL: Dr. Krishnan-Sarin?

16 DR. KRISHNAN-SARIN: Thank you. Suchitra
17 Krishnan-Sarin from Yale. I have two questions. One
18 is related to the other constituents in this product.
19 One of the things we are learning from e-cigarettes
20 especially -- and I'm sorry to keep bringing this up,
21 but they are in the marketplace, and they're learning a
22 lot from them -- is that there are people who are

1 allergic to some of the ingredients which are in
2 e-cigarettes, like propylene glycol, which is something
3 that I did not realize until I started working in this
4 area.

5 I also noticed that you have about 10 percent
6 alcohol in it as a solvent, I'm assuming, in this
7 liquid. I think it would be good to know, from the
8 standardized exposure paradigm that you're proposing
9 people use, approximately how much of these are
10 actually delivered to the people; in some model how
11 much alcohol do they actually absorb because some
12 research from e-cigarettes have shown that people can
13 deliver a lot of alcohol to the point of almost feeling
14 intoxicated.

15 As I said, propylene glycol issue is something
16 that came up in my son's school with a teacher who
17 inhaled something that somebody else sprayed and had a
18 severe allergic response. So it's just a good idea to
19 think about these things and also maybe put some
20 information on the label regarding the potential for
21 these issues.

22 My second question was a more general

1 question. Has GSK done any work with smokers, focus
2 group work, qualitative work, to ask them if they want
3 such a product and whether this product would provide
4 any kind of an advantage for them over and above the
5 products which exist on the market?

6 DR. MISHRA: Thank you for those questions.
7 Raj Mishra, Johnson & Johnson. I'll address the first
8 question. Slide 3 up, please. This is a question
9 relating to the amount of ethanol. As you can see, the
10 amount of ethanol per spray dose corresponds to
11 7.1 milligram, which is about 0.009 pure ethanol.

12 So the maximum recommended usage, which is 64
13 doses per day, which most people don't use, they would
14 ingest about less than 1 teaspoon of a wine with 12
15 percent alcohol content. So to inform consumers, the
16 product is clearly labeled with the ethanol content.

17 Your second question I think is around what
18 GSK has done with consumers, so I'll invite Ken to
19 address that.

20 MR. CHRISTENSEN: Ken Christensen, GSK. Thank
21 you for the question. Yes, one of the benefits, I
22 suppose, of taking a while to develop these products is

1 you have plenty of time to do really rigorous consumer
2 testing. And we know, with a very high degree of
3 confidence, that consumers who are out there,
4 particularly people who have tried unsuccessfully to
5 quit, are waiting, number one, for something new
6 because there's hope when there's a new option; maybe
7 this one will work for me.

8 But number two, people have said very
9 clearly -- or I should say many people have said very
10 clearly that they wish they had something that was more
11 discreet, number one, than other oral formats,
12 recognizing that patches are quite discrete. You put
13 them under your clothes and you're done. But I think
14 the more interesting thing that they've told us is they
15 don't feel that the products that are out there at the
16 moment get to work as quickly as they'd like, not
17 meaning relief, but they all require a bit of work to
18 even feel whether or not there is any real benefit, but
19 to feel like something's happening.

20 When a craving strikes somebody, it often
21 feels like a ton of bricks is dropping from above their
22 head. And the reason that this product has appealed to

1 so many folks in focus groups is because it is a
2 quick-release spray and they feel like they are able to
3 do something very quickly as soon as the craving hits
4 to try to get through it. So there is a real need, in
5 our opinion, on the part of people who are still trying
6 to quit for a product that works the way this one does.

7 DR. ZORICH: May I ask, is that data somewhere
8 in here in this package?

9 MR. CHRISTENSEN: I don't believe that we
10 included it in our briefing book. It's certainly
11 something that we could follow up on if the committee
12 desired.

13 DR. NEILL: Thank you.

14 So I have a question. Richard Neill. I have
15 two of these containers. One is empty because I've
16 used it, and the other is not. If I have them both on
17 the ground, how would I know which one is empty?

18 DR. MISHRA: I'll invite Andrew Myers to help
19 address that. Thank you.

20 DR. MYERS: Andrew Myers, J&J. So as you have
21 seen by your sampling this is a plastic container. It
22 is black. You can't look and see how much is in there.

1 Two ways we think people will monitor how much they've
2 used: one would be counting their sprays and days, and
3 the other is you can hold it, shake it, in the example
4 you have, to feel which one's heavier and which one is
5 shaking or has a liquid sound.

6 DR. NEILL: So we would guess, an educated
7 guess, but a guess.

8 DR. MYERS: I think based on your perception
9 of hearing, I suppose.

10 DR. MISHRA: And if I might add from our
11 postmarking experience out to the U.S., I think this
12 has not been an issue because we haven't received many
13 major complaints around people unable to do that,
14 whether they're struggling with that. I mean,
15 occasionally we may have had some.

16 DR. NEILL: Richard Neill. I guess I'm
17 thinking about the asthma inhalers and the kind of
18 standard way that we can pull them out and throw them
19 in a bowl of water, and tell pretty closely that
20 they're empty, or many of them now have counters. I
21 didn't know if there was some secret way to tell.
22 Okay.

1 DR. MISHRA: Thank you.

2 DR. NEILL: Very good. Are there any other
3 clarifying questions for our sponsor? We've done a
4 phenomenal job getting them, so both Dr. Parker and
5 Dr. Pruchnicki.

6 Dr. Parker?

7 DR. PARKER: The question was on how do I keep
8 up with how many I've done a day? How do I count to 64
9 and know that now I'm over 64. and what we know about
10 people's ability to keep track of how many they -- if
11 the maximum is 64 a day, how do we know where we are
12 and keep up with it? And if we decide to interact with
13 a book and put it down, how do we do that? How do I
14 keep up with how many?

15 Then the other question I have is,
16 normally -- do we know that smokers really normally
17 smoke at a certain time and know it? Like you normally
18 smoke, so you're going to take one, then you wait a
19 couple minutes, then you take a second one. But what
20 if you normally sometimes smoke more than two
21 cigarettes in an hour, and sort of how that plays out
22 in terms of -- maybe sometimes you need 12 puffs of

1 this in an hour.

2 Did these kind of things ever come up in
3 testing? Do we have any sense of how that plays out?

4 DR. MISHRA: So I think there are two parts to
5 your question. One is how do people keep track, so I'm
6 going to invite Ken to address that. And then we'll
7 come to your second part of the question later, and
8 probably Dr. Nides will be able to put that in context.
9 Thank you.

10 MR. CHRISTENSEN: Ken Christensen, GSK. Thank
11 you for the question, Dr. Parker. I brought my phone
12 up because we've done -- or we're planning on doing two
13 things to help make the tracking process easier for
14 people. Number one, in the user guide, there's an old
15 fashioned pen and paper type chart that would allow
16 someone to keep track of the number of times that
17 they've used this spray on a given day during a given
18 week.

19 But we've also developed, as I referenced
20 earlier, this mobile app. It's still in the early
21 days, but one of the key features is literally at the
22 click of a button, you can log a craving. You can also

1 clarify how intense the craving was. There's a geo
2 location feature that will automatically track for you
3 if you so choose where you experienced the craving.
4 But it will also allow you to log every single time you
5 use an NRT product if that's what you're choosing to
6 do, whether it's a lozenge, or certainly if we were to
7 get approval for the spray, we would build that in as
8 an option.

9 You literally touch the button, and then at
10 the end of the day, or at any point if you're
11 interested, you can see a simple graph of, oh, okay, so
12 I'm on my 15th spray of the day. I've used 75 this
13 week, et cetera, et cetera. So we've tried, and we
14 will continue to try to encourage people to embrace
15 this particular app. It's simple. It's designed to
16 work with the way they live their lives, and hopefully
17 that will help them keep track of how they're using the
18 product.

19 DR. PARKER: Whose data would that be?

20 MR. CHRISTENSEN: That is a good question. I
21 wish I were the data privacy expert. The one thing I
22 can reassure you is that we take it incredibly

1 seriously. I would like, if you don't mind, just
2 following up with some of my more informed colleagues,
3 and I can confirm for you exactly who would own the
4 data. But unless we were given explicit approval by
5 the user, the data would remain completely confidential
6 and would be their data, but let me follow up if you
7 don't mind. Thank you.

8 DR. NEILL: Dr. Pruchnicki?

9 DR. PRUCHNICKI: Maria Pruchnicki. I have a
10 thought and then a question, and I think my thought
11 follows up to Dr. Parker's comment. I think there are
12 certainly patients, in my experience and in my
13 clinic's, that would do a lovely and meticulous job of
14 recording those doses, and would be able to not only
15 use the product safely, but they would be able to
16 follow step 2 and actually make sure that they are
17 having their use of the product. But I have an equally
18 large, maybe even a larger contingent, where that would
19 be incredibly challenging.

20 So I think while your techniques or your
21 strategies are very admirable, I think they fall far
22 short of where most of my patients can live their

1 lives. So that's my feedback in that regard.

2 The other question that I have is, one of the
3 advantages that you have mentioned of this particular
4 product is that it's flexible, it's at the moment that
5 a craving might strike. But you also are going to add
6 a statement on the product label, or on the package
7 label, saying that they need to avoid eating and
8 drinking within 15 minutes of using the product, which
9 seems to take away that flexibility. And if it is in
10 fact a real concern, then that seems to me like a large
11 problem in terms of using this product or recommending
12 it for a patient, or a patient self-selecting it on
13 their own when they have those limitations. So I'm
14 interested in your thoughts on that.

15 DR. MISHRA: So I think as the dosing
16 recommendation goes, they can use one spray, and if
17 within a few minutes they don't get any relief of
18 craving, they can use a second one. So that could
19 happen fairly quickly. So assume they've got their
20 unit dose, which gives them the relief. The
21 recommendation to not drink or eat anything within 15
22 minutes, that is just to kind of avoid -- as I said, if

1 they drink some acidic drink or anything, it might
2 reduce the effectiveness of the amount of nicotine
3 which is getting absorbed.

4 So from a pharmacological perspective, we
5 don't feel that will interfere in any way with the kind
6 of effective use of the product by the user.

7 DR. NEILL: Thank you. I think we're going to
8 take one more question before we ask Dr. Michele to
9 charge the committee. Dr. Krinsky?

10 DR. KRINSKY: Yes, thank you. Let's assume
11 you have a patient that used the product, followed the
12 directions, and got to about day 80, and relapsed, and
13 started smoking again, and this patient decides they
14 want to start from scratch with the 64 sprays per day;
15 is it safe to do that? Do we have any data on repeat
16 cycles using the product?

17 DR. MISHRA: I'm going to invite Dr. Nides to
18 address that.

19 DR. NIDES: Mitchell Nides, LA clinical
20 trials. We see this quite frequently when people
21 relapse, and then they go back to using the nicotine
22 replacement product. Starting at the beginning,

1 they're still getting the same amount of nicotine.
2 There's basically no difference than when they were
3 starting before. And most people are going to use
4 enough to feel comfortable.

5 Getting to some of the issues that you were
6 raising, I was a smoker myself, as you know. I've
7 dealt with thousands and thousands of smokers. Smokers
8 know their own cravings. They know when they want a
9 cigarette, and they're going to know how to use this
10 product. Once they get used to it, they're going to
11 know how to use it in order to manage their cravings,
12 just the way they know how to manage their cigarettes
13 to deal with their cravings.

14 Some of those cravings come from not having
15 nicotine for a long period of time because the
16 half-life is 2 hours. Some of those cravings come from
17 they just got in a stressful situation. Others come
18 from they're driving down the street and they see a
19 7-Eleven where they usually buy their cigarettes.

20 So the cravings come at different times, and
21 smokers know when they're going to reach for it, and
22 they'll know when to reach for this product as well.

1 So I think the intuitiveness of the product, along with
2 the fact that they can spray it fairly quickly and get
3 some relief is going to find a nice place in the
4 armamentarium to help smokers quit.

5 DR. NEILL: Ms. Thomas?

6 MS. THOMAS: Hi. Jill Thomas, patient
7 representative. I had a question about the dosing
8 regimen. It's a 3-step process. I was wondering if
9 for every step down you take, if there would be a
10 withdrawal from that, going from a certain milligram to
11 a different milligram, and what the benefit would be
12 for that versus just kind of quitting cold turkey or
13 using another NRT.

14 DR. MISHRA: Thank you. I'll invite Dr. Nides
15 to address that, please. Thank you.

16 DR. NIDES: Mitchell Nides, LA clinical trials
17 a very good question. People tend to know when they're
18 ready to wean down in terms of the steps. Slide 1 up,
19 please. All of the products that are out do have a
20 weaning schedule. But again, that weaning schedule is
21 somewhat flexible based on how they're doing, how
22 they're doing at the time.

1 If they're going to start weaning down, and
2 they may feel a little bit of withdrawal, they might
3 hold off a little bit longer, and then they do
4 eventually tend to wean down. We have some data from
5 the compliance data, from the 38 study; in fact, from
6 both studies. If we can look at the median use of the
7 product from week 1 all the way down through week 12,
8 if we can show that.

9 Slide 1 up. Here, you can see for both
10 the -- this is a kind of busy slide, but both for the
11 11 study and for the 38 study, you can look to see what
12 the median number of sprays per day was as reported by
13 the subjects. If you look primarily at those that are
14 in the box, you can see those that were abstinent. And
15 they start off using -- let's look at the 38 study.

16 They started off using 10.8 sprays per day,
17 and they slowly come down. By the time you get to week
18 4, it's 6.8 sprays per day. By the time they get to
19 week 6, it's 5.5 sprays per day. And then by the time
20 you get to week 12, it's 3.4.

21 Most smokers during the first 2 weeks is where
22 they're feeling the majority of those really, really

1 strong cravings, and then it begins to taper off. The
2 time between when they want a cigarette all of a sudden
3 gets longer. I remember I was quitting. I was saying,
4 "Oh my God. I've gone an hour, and I didn't think
5 about a cigarette." It was like the greatest victory
6 ever. So those times will get longer spaces in
7 between, and you do see that they naturally come down.

8 DR. NEILL: Thank you. We will now turn our
9 attention to the task at hand, the careful
10 consideration of the data before the committee, as well
11 as the public comments.

12 Dr. Theresa Michele will now provide us with a
13 charge to the committee.

14 **FDA Charge to the Committee - Theresa Michele**

15 DR. MICHELE: Thank you, Dr. Neill. Before I
16 get started, I wanted to, once again, express our
17 appreciation to all of the members of the committee.
18 You are being given a difficult task. If it were an
19 easy task, we wouldn't have asked you to come here. So
20 we greatly appreciate all of your expertise, and we
21 really look forward to some rich conversation.

22 Over the next few minutes, I'll focus on the

1 questions that you're being asked to consider, and I'll
2 try to provide some context on which they were written.
3 Once again, we come back to the topics for discussion,
4 all of which we'd like for you to consider in the
5 setting of over-the-counter use. These focus on the
6 efficacy, the safety, and the potential for abuse and
7 misuse of nicotine mouth spray, based on the currently
8 proposed labeling.

9 To help set up the over-the-counter context in
10 which this drug review is taking place, I want to
11 remind you of the expected characteristics of over-
12 the-counter drugs, namely that they can be adequately
13 labeled, such that the consumer can self-diagnose,
14 self-treat, and self-manage the condition being treated
15 without the intervention of a healthcare practitioner.
16 Also, the drug has a low potential for abuse and
17 misuse, and the safety margin is such that the benefits
18 of over-the-counter availability outweigh the risks.

19 Before we get to the questions, I also want to
20 remind you of the laws governing FDA decisions of
21 approval or non-approval, which are relevant to how we
22 ask you to consider the question. Of note, these laws

1 apply equally to prescription products and
2 nonprescription products. The standards for efficacy
3 and safety that are set out in the CFR are the same.

4 The Code of Federal Regulations, or the CFR,
5 states that FDA will approve an application after it
6 determines that the drug meets the statutory standards
7 for safety and effectiveness, manufacturing and
8 controls, and labeling. Of note, we are not discussing
9 manufacturing and controls or product quality in this
10 meeting, and those considerations may affect the
11 ultimate approvability of an application.

12 The regulation also mentions that there are
13 many kinds of drugs that are subject to the statutory
14 standards, and the wide range of uses of these drugs
15 demand flexibility in applying those standards. Thus,
16 FDA is asked to exhibit scientific judgment, and the
17 aim of this meeting is to get your views and scientific
18 judgment on the safety and effectiveness of nicotine
19 mouth spray for over-the-counter use to help guide our
20 decision making on these issues.

21 Let me now discuss the standards for efficacy
22 and safety. Efficacy standards are shown on this

1 slide. The language is from a CFR section on refusal
2 to approve an application. One clause to note related
3 to this meeting is substantial evidence, meaning that
4 efficacy must be certain and without any doubt. We ask
5 you to vote yes or no on the efficacy question based on
6 your conclusion as to whether or not nicotine mouth
7 spray is effective as a smoking cessation aid in the
8 over-the-counter setting.

9 The standards for safety are shown on this
10 slide, and the language is from the same CFR section.
11 The regulatory language in these three paragraphs boils
12 down to four safety reasons for non-approval. First,
13 that this submission does not have adequate tests to
14 assess safety; second, that the product has been shown
15 to be unsafe; third, that the submitted results do not
16 show that the product is safe; or fourth, that there
17 are insufficient information in the submission to
18 determine whether or not the product is safe.

19 Note also that all of these safety standards
20 are relative to the labeled use of the product, which
21 in this case is for the consumer to use without the
22 intervention of a healthcare professional.

1 This brings us to the questions. The first
2 question is a discussion of efficacy, and in your
3 discussion, we ask you to please consider the
4 differences and results between the two efficacy
5 studies that were presented.

6 In the second question, we ask you to consider
7 the results of the label comprehension study and
8 discuss the implications of these results relative to
9 efficacy in the over-the-counter setting. Since
10 consumers don't have a doctor or other healthcare
11 professional giving them instructions on how to use the
12 product, consumer understanding of labeling is
13 especially key to ensure safe and effective use.

14 The third question is the voting question for
15 efficacy. Note that you are voting on the proposed
16 indication in the over-the-counter setting. If you
17 vote no, please discuss what further data should be
18 obtained. Now, for the voting questions, we're
19 especially interested not only in whether you're voting
20 yes or no, but in your reasons for that, and we take
21 that into consideration as we consider the input that
22 we receive in this meeting.

1 The fourth question is a discussion of general
2 safety, and the fifth question asks you to discuss the
3 potential for abuse or misuse of nicotine mouth spray
4 both by the adult population, who might use the product
5 for smoking cessation, and also by youth, who might be
6 using the product for recreational purposes. In your
7 discussion, please consider the pharmacokinetic profile
8 of nicotine mouth spray and any other characteristics
9 that you feel are different from other already approved
10 over-the-counter products that you think might impact
11 this question.

12 The sixth question is a voting question for
13 safety in the over-the-counter setting, taking into
14 account both general safety that you discussed in
15 question 4 and also the potential for misuse and abuse.
16 If you vote no, please outline what further data you
17 think should be obtained to demonstrate safety.

18 Finally, question 7 is where we ask you to
19 bring it all together to balance the scales of safety
20 and efficacy for the proposed over-the-counter smoking
21 cessation indication. As part of your balancing act,
22 you may wish to consider the responses that you gave to

1 the voting questions number 3 and 6 since this question
2 is essentially the sum of the two. So in other words,
3 in order to vote yes on this question, we expect that
4 you would have also voted yes for the two previous
5 questions.

6 With that, I will turn the meeting back over
7 to the ever efficient Dr. Neill for further discussion.
8 Thank you.

9 **Questions to the Committee and Discussion**

10 DR. NEILL: Why, thank you, Dr. Michele.

11 We will now proceed with the questions to the
12 committee and panel discussions. I would like to
13 remind public observers that while this meeting is open
14 for public observation, public attendees may not
15 participate except at the specific request of the
16 panel. We will be using an electronic voting system
17 for this meeting. Once we begin a vote, the buttons
18 will start flashing and will continue to flash even
19 after you have entered your vote. Please press the
20 button firmly that corresponds to your vote. If you
21 are unsure of your vote or you wish to change your
22 vote, you may press the corresponding button until the

1 vote is closed.

2 After everyone has completed their vote, the
3 vote will be locked in. The vote will then be
4 displayed on the screen. The designated federal
5 official will read the vote from the screen into the
6 record. Next, we will go around the room, and each
7 individual who voted will state their name and their
8 vote into the record. You can also state the reason
9 why you voted as you did if you wish to. We will
10 continue in the same manner until all questions have
11 been answered or discussed.

12 We've had the questions read to us. Are there
13 any questions about the wording of the questions?

14 (No response.)

15 DR. NEILL: Hearing none, we're going to dive
16 in. Let's begin with the first discussion question
17 that's displayed. Discuss the efficacy of nicotine
18 mouth spray, 1 milligram per spray as an
19 over-the-counter OTC smoking cessation aid. Consider
20 the differences between the efficacy data from
21 studies 11 and 38.

22 I am a family physician. That makes me a

1 generalist. That makes me look at everything in broad
2 swaths. Fortunately, we have many specialists on the
3 committee, but my broad swath and what I would offer at
4 the outset is that the efficacy study 11 showed both
5 statistical and clinically significant evidence of
6 efficacy; that study 38 showed statistically
7 significant, albeit low, evidence of efficacy; and that
8 there is likely to be discussion about whether the
9 significance of study 38 is clinically significant.
10 And I'm hopeful that we can get a broad variety of
11 views related to that, why you think it is or isn't, to
12 inform FDA.

13 Anybody care to start? Dr. Curry?

14 DR. CURRY: So I would have a little bit -- I
15 would add a term, which is "public health
16 significance," not just clinical significance. I think
17 from that perspective, study 11 does show the potential
18 for public health significance.

19 DR. NEILL: Dr. Farber, and then Dr. Zorich?

20 DR. FARBER: Neil Farber, UC San Diego. I
21 have concerns about the difference between the two
22 studies. There's something quirky about it, and the

1 quirkiness could be based on a different population for
2 some reason. It could be differences in society
3 between the two studies, or it could be methodology as
4 GSK pointed out. Or my concern is it could be the
5 inhaler itself. There's something about the inhaler
6 that's making patients not be as interested in using
7 it. It's cumbersome; it's whatever, and I don't see
8 any data about that. Is it clinically significant?
9 Small amounts like that, no. You look at a big
10 population, yes, but I have concerns about the
11 difference.

12 DR. NEILL: Dr. Zorich?

13 DR. ZORICH: I'm glad you used the word
14 "quirky" because there's something else that kind of
15 piqued my interest. And we don't have to go very far
16 to look for it. We could just look in the FDA's
17 presentation from this morning on the efficacy. I have
18 expertise in clinical trials. I don't have expertise
19 in this area. But I am really impressed by something
20 that I see that's odd, and it isn't necessarily these
21 two trials that the sponsor brought.

22 If you look at the FDA's own slides and you

1 look at slide 3, which is source, FDA files, you'll see
2 there in the over-the-counter switch bullet, at the
3 very last sub-bullet, consistent findings of continuous
4 abstinent rates, CAR, weeks 2 to 6, in the range of 15
5 percent to 20 percent on active treatment.

6 Is that okay? Do people see where I'm talking
7 about? I'm on slide 3 of the FDA's deck on efficacy

8 FEMALE VOICE: Efficacy and safety data?

9 DR. ZORICH: Yes. The FDA's deck on efficacy,
10 slide 3 third bullet and the third sub-bullet. And it
11 says that the source is the FDA files. So it says,
12 "Consistent findings of CAR, weeks to 6 and range of 15
13 to 20," and that was presented today.

14 Then we go to slide 28 in the same deck, and
15 the FDA asked us to consider as a reference an NRT
16 study with a lozenge. And in that study, the placebo
17 rate is 30 percent. So in that study that the FDA is
18 showing us, which had remarkable efficacy -- I mean,
19 whatever happened in that study, let's get it out
20 there -- the placebo is 10 percent over than what the
21 FDA is a consistent expected rate of efficacy.

22 So what that tells me is that I don't think we

1 have to be overly concerned about the product. It does
2 tell me that there are a lot of factors that influence
3 the outcomes in these studies that we don't understand
4 well, and you can have a study that gives you
5 disappointing but statistically significant results,
6 and then you can have another study that gives you just
7 as unexpected results, and yet it's not clear why.

8 So, to me, I really have a tough time making a
9 decision that study 38 is -- the FDA said it was an
10 unsuccessful study. I think you have to go by the
11 definition of what success is, which is prespecified
12 endpoints did they meet. And while the study results
13 were perhaps disappointingly low, I think that it met
14 the endpoints.

15 DR. NEILL: Dr. Curry and then Dr. Shoben.

16 DR. CURRY: I just want to understand. I
17 understand that the types of studies that can be done
18 for switching from an approved prescription to an OTC
19 are different than direct to OTC, so some of these
20 studies that have higher quit rates were switched.
21 They were going from approved, so they were not
22 done -- design-wise, they were different than this

1 study. I don't know if that's quirky or not, but --

2 DR. NEILL: It's different.

3 DR. CURRY: It's different, yes.

4 DR. WINCHELL: I can speak to that if people
5 are curious.

6 DR. NEILL: Please.

7 DR. WINCHELL: Sure. In the numbers from
8 slide 3 that you refer to, that is a summary of the
9 studies that were done to support Rx to OTC switch. It
10 was quite surprising how consistent the results were.
11 The studies were designed many different ways; some
12 open label, some controlled, some based on surveys of
13 people who'd filled a prescription; many different
14 designs, not all of which would pass muster in our
15 current way of looking at data. But it was quite
16 consistent what the results were across three different
17 transdermals and gum -- four different transdermals.
18 One was a little less.

19 As Dr. Curry said, the lozenge trial was
20 direct to OTC development. We certainly have seen
21 many, many smoking cessation studies over the years.
22 That is a high placebo rate compared to some, so that

1 was a pretty impressive result for that study, and
2 perhaps the explanation -- the difference between what
3 you saw in that slide and what you saw in slide
4 number 3 is that those are two different types of
5 studies, or actually many different types of studies.

6 DR. NEILL: So I've got Dr. Shoben,
7 Dr. Hatsukami, and then Dr. Nelson. Dr. Shoben?

8 DR. SHO BEN: Sure. Abby Shoben. I just
9 wanted to say for the record, I think study 38 was a
10 really nicely done study to simulate the effect of what
11 this would look like in the over-the-counter setting.

12 Just sort of taking anyone who vaguely said
13 they might want to quit, give them the product and see
14 what happens, I think there are two possible
15 explanations for the really low placebo quit rate. One
16 is to say that this group in this study just was, for
17 whatever reason, less ready to quit. You see
18 dramatically different quit rates, in different
19 populations, with different things. I'm a
20 biostatistician, so I won't pretend to speculate on
21 those reasons, but you do see variety of quit rates.

22 So this group just was very unready to quit,

1 in which case we do see efficacy because there was the
2 higher quit rate in the active drug arm. I think the
3 other possible explanation is that you aren't getting
4 any sort of placebo effect from the device in the sense
5 of this device, for whatever reason, people aren't
6 using or aren't thinking it's working or something like
7 that. So you'd have sort of a low potential placebo
8 effect from this device as well, compared to like a gum
9 or a patch, where you can give them a placebo and
10 potentially get some benefit from that.

11 DR. NEILL: Thank you. Dr. Hatsukami?

12 DR. HATSUKAMI: I've been doing research in
13 the area of nicotine addiction for almost 40 years, I
14 think, and I think that one of the real concerns I had
15 is the existing nicotine replacement products really
16 can't compete with the cigarette products that they're
17 trying to replace. Part of it is the fact that there
18 is a slow absorption rate. They're not getting as much
19 nicotine in some cases as they do from cigarettes.

20 So I really applaud the fact that there might
21 be a potential medication that has a more rapid
22 delivery of nicotine and that can relieve craving, as a

1 result, more rapidly. I guess I'm not as disturbed
2 about the differences in study 11 compared to study 38.
3 I think study 11, you do see a higher rate primarily
4 because there was psychosocial behavioral treatment
5 that was administered with the careful instruction in
6 terms of how you use the product. And the literature
7 clearly shows that if you add a psychosocial treatment
8 along with a medicinal treatment, you're going to have
9 higher success rates.

10 I think it is somewhat disappointing that the
11 rate of success in 38 was not as high as what we would
12 like to see, but that's in the context of having very
13 minimal instructions in how to use the product, as well
14 as minimal behavioral support. And I do think that you
15 are treating a more difficult population than what
16 we've treated in the past. I find that in my own
17 research that it's harder. It's more of a challenge to
18 get people to quit smoking.

19 I think in the context that GSK is thinking
20 about providing more extensive psychosocial treatment,
21 in addition to video guidance in terms of how you use
22 the product, that the rates may not be as low as might

1 be indicated in this particular study. But I also
2 think, as Dr. Curry has pointed, that we have to think
3 of public health, too, and I pointed this out in my
4 question, that even a 3 percent difference can be
5 substantial in terms of the number of people that it
6 would affect in terms of getting them successful to
7 quit smoking.

8 So I think we have to think in terms of the
9 context of how many people are smoking, how many of
10 them are dying of smoking-related disease. And to
11 offer them an option of another treatment that may be
12 effective for some people I think is a good step in the
13 right direction.

14 DR. NEILL: Thank you. Dr. Nelson?

15 DR. NELSON: Much of what I want to say has
16 already been set. However, I will also emphasize that
17 it looks like the key difference between 11 and 38 was
18 the psychosocial side because nothing else is
19 different. And the low level of placebo effect was
20 really striking in that particular study.

21 So while this is over the counter, many of
22 these people will be working with physicians, and if a

1 physician can recommend that they get the drug, they
2 can potentially supply the psychosocial social side of
3 it, give them the support which would increase the
4 efficacy of the drug. So that's another element adding
5 to the potential efficacy of this particular delivery
6 system.

7 DR. NEILL: Thank you. Dr. Krishnan-Sarin?

8 DR. KRISHNAN-SARIN: So let me just say that I
9 don't have a problem with the medication per se, and
10 the fact that it is a nicotine mouth spray, and the
11 fact that it might be useful for smokers if they want
12 to quit smoking. I really don't have a problem with
13 that. I think I would be willing to accept the fact
14 that it will probably work and that smokers will
15 probably benefit from having this. However, I am
16 struck by the fact that there are such huge differences
17 between a study which actually provides more structured
18 behavioral counseling and one that just delivers it
19 openly to people, and my question is twofold.

20 Number one, whatever we put out there should
21 have maximum efficacy. Why do we want to go with a
22 model, like over the counter, where people are not

1 getting the efficacy that they need from this product,
2 when it's already shown that if it's given in a
3 different format, it can actually work better?

4 I guess that's the part I'm struggling with.
5 I'm not questioning the efficacy from this spray; I'm
6 sure it will work well. I'm questioning the
7 over-the-counter aspect of this. And let's also
8 remember -- I know people are not going to like this,
9 but nicotine replacement therapies were not over the
10 counter when they first came out. They were delivered
11 as prescription aids for a very long time until we
12 showed they work, and they were safe to use, and they
13 didn't produce any effects, and then we moved them to
14 over the counter. So it's just good to keep a
15 historical perspective in mind, too.

16 DR. NEILL: Thank you. Dr. Farber?

17 DR. FARBER: Neil Farber, UC San Diego.
18 There's another aspect of study 38. Everybody's
19 talking about the psychosocial support that patients
20 got, and that's extremely important. But there's
21 another aspect of what was done with 38, and that was
22 structure about how to use the thing, how to taper off,

1 et cetera, and patients were counseled about how to do
2 that.

3 We're going to get to it I'm sure in
4 question 2 in a minute, but my concern is that looking
5 through it, I had questions about how do I do this if I
6 were a patient. I'm sure patients had a lot of
7 questions about how do I do this. And I think that's
8 shown in things like the fact that they were using less
9 sprays than they would be expected to. Perhaps they
10 thought it was
11 somehow you spray, and you can smoke, and you'd still
12 be able to stop things, and things like that.

13 So I think there are more things that need to
14 go into the labeling, perhaps, that would help patients
15 with this.

16 DR. NEILL: Dr. Roumie?

17 DR. ROUMIE: I agree, and I think the issue of
18 whether or not it helps over and above nothing, if
19 nothing else, you can take study 11 and say, yes, it
20 helps over and above nothing. But I think it really
21 does boil down to what discussion question number 2 is,
22 and I know we're not really there. But the label is

1 unclear, and to me, that is really one of the key
2 elements for the OTC format.

3 I was very struck by the data that was
4 presented that if you had to integrate step 1, and
5 step 2, and step 3, it's basically a coin flip that one
6 patient would get it and one patient wouldn't, and that
7 is very telling for me. That says it's not necessarily
8 ready, that drug facts label and the directions for
9 use, to go out prime time.

10 DR. NEILL: I do have Dr. Hatsukami, but
11 before I call on you, I would like to acknowledge the
12 presence of my fellow non-speaking introverts,
13 Dr. King --

14 (Laughter.)

15 DR. NEILL: -- and Ms. Mack-Brooks. And I've
16 never met an introverted Italian, but Dr. Di Francesco,
17 you're being very quiet, and I want to make sure that
18 you understand that we're anxious to have your
19 discussion and contributions, unless of course you feel
20 things have already been said. So I'm offering you the
21 opportunity now; if not, please know that I will go
22 around the group, generally, later as well, and I want

1 to encourage you to discuss, just get our attention.

2 Dr. Hatsukami?

3 DR. HATSUKAMI: Dorothy Hatsukami. I guess my
4 feeling in terms of whether it should remain
5 prescription only, it's the whole issue of reach again.
6 Certainly, when you have over the counter, more people
7 are going to make a quit attempt. So I'm not really
8 sure whether we should go back to thinking about having
9 this as a prescription only, especially in light of the
10 fact that there are 45 countries that have this as a
11 drug, as a medication, and half of those countries are
12 self-selecting.

13 So it seems to me that there's sufficient
14 safety data, at least, to show that it's not going to
15 create a real major concern. I don't want to go
16 backwards in not making this product more available to
17 people.

18 DR. NEILL: Thank you. Dr. King?

19 DR. KING: Tonya King. I think
20 biostatisticians are less likely to speak up in these
21 settings.

22 (Laughter.)

1 DR. KING: We like to sit back, and observe,
2 and collect all the data, and then form our opinion.
3 But I would just like to say I think it's clear that
4 statistical significance is not the only factor to
5 consider here. And in my opinion, these two studies,
6 really, the answer and the question of OTC
7 appropriateness is really only being answered by
8 study 38. I think study 11 is very interesting, but
9 it's very different. It's in a different population,
10 different control, and I think that it's difficult to
11 answer the question based on that study.

12 I also think some of the discussion, I think
13 we want it to work. I think the idea that there's a
14 quicker release, and all of the reduction in puffs or
15 whatever is impressive, and that it's, in theory,
16 great, but if it's not helping people to quit smoking,
17 then that's important to consider. So I think there's
18 a little disconnect between the results, and maybe we
19 want to make assumptions that by putting this right
20 into the over-the-counter market, things will be better
21 based on study 11, but I think there's a missing piece.
22 Thank you.

1 DR. NEILL: Thank you. Dr. Di Francesco?

2 DR. DI FRANCESCO: Lorenzo Di Francesco,
3 Emory. My comment is to kind of tag along with some of
4 the other comments about study 38, in that I'm
5 interested, and I'm used to seeing studies with a lot
6 larger numbers.

7 So I'm struck by the results in 38 with 30
8 people in the treatment group and 15 people in the
9 placebo group, and making a decision about the efficacy
10 of a product that at 6 weeks and getting somebody to be
11 abstaining is challenging Because I'm looking at
12 whether or not they're actually going to quit; 6 weeks
13 later, and 6 weeks later, and 6 weeks later are they
14 going to relapse? Are they just going to be yo-yoing
15 through different treatment strategies?

16 So it would be nice if there were studies with
17 a little bit more length to show that, actually, it was
18 sustained, or that the numbers were a little bit
19 bigger. Those are some of the challenges that I have
20 with study 38.

21 DR. NEILL: Thank you. We're going to go to
22 Dr. Krinsky, then we'll come back, Dr. Krishnan.

1 DR. KRINSKY: Thank you. Regarding the two
2 studies, I do think that, as was mentioned earlier,
3 study 38 is best reflective of what we're going to see
4 in the actual community setting. I think it's
5 important to remember that based on the guidelines for
6 approving a product for OTC use, we can't assume the
7 patients are going to get any sort of behavioral
8 modification because the product needs to be approved
9 with the thought that they can manage the product
10 entirely without the intervention of a healthcare
11 professional.

12 DR. NEILL: Dr. Krishnan?

13 DR. KRISHNAN-SARIN: I just wanted to respond
14 to what Dorothy said. My thought was certainly not
15 that it should become a prescription product. It's
16 more that I feel that if study 38 had been done with
17 more guidance around how to use the product and more
18 support behaviorally, that we probably would have had
19 better outcomes.

20 So I'm just suggesting that perhaps that could
21 be something we would like to see. I don't know how
22 this process works, but if there is any evidence of

1 that or if that's new data that could be generated,
2 that would be great. I was not suggesting going down
3 the prescription road because I understand the reach
4 issue.

5 DR. NEILL: Dr. Curry, then Dr. Pruchnicki?

6 DR. CURRY: I think the comment about the
7 importance of behavioral support is important, and I do
8 think that that contributed to a difference between the
9 two studies. I would question whether -- I believe
10 that smokers actually can self-select or select into
11 behavioral treatment that doesn't have to be delivered
12 one on one.

13 From GSK and other NRT and pharmacotherapies
14 for smoking cessation, companies have worked very hard
15 to develop behavioral programs that are state of the
16 art, and I think there's data out there, including in
17 Cochrane reviews, that show that self-help materials
18 when used can make a difference.

19 So with all of the pieces that go with this
20 that weren't included, if you could go back in time and
21 redesign study 11, I would have tested it with all of
22 those supports because they're not that hard to get to,

1 and people use apps all the time, and so on and so
2 forth. So I'm not sure that the only method for that
3 would be one on one or the kind of intensive behavioral
4 support that some of the earlier pharmacotherapy
5 studies had.

6 DR. NEILL: Dr. Pruchnicki?

7 DR. PRUCHNICKI: Maria Pruchnicki. A couple
8 of comments that my colleagues to my left and my right
9 have said really resonate, and I think are worth
10 repeating. Dr. Roumie mentioned that compared to not
11 treating with a nicotine replacement product, the
12 nicotine mouth spray is likely to help folks. But the
13 comparison should not be to nothing. It should be to
14 the products that are available as well, because we do
15 have products that are available that may be more
16 effective in the real-world setting, at least based on
17 what we know so far.

18 I think also Dr. King mentioned that there's a
19 lot about this product that is appealing, and I would
20 like to believe that we have innovative products, and
21 that we're continuing to make strides in improving
22 formulations, but I'm not sure we're quite there yet.

1 And I would like to see how do we optimize this
2 product, maybe optimize the directions, and optimize
3 some of the studies that are done in the real-world
4 settings so that we can really put something out there
5 that is not only effective but maybe just as good as,
6 or better, than what's already there.

7 DR. NEILL: Thank you. Dr. Parker?

8 DR. PARKER: Just a reiteration of mostly what
9 we've heard, I think we have a unique opportunity,
10 because of the structure of the two studies that we're
11 looking at, to see such big differences. I think it
12 underscores, in terms of efficacy and the question
13 related to bringing it to market for efficacy, in an
14 over-the-counter setting, that without the other
15 support, though it did not cross zero, it's set at
16 zero, the final numbers.

17 So I love the discussion about absolute risk,
18 and relative risk, and clinical significance versus
19 public health significance. It underscores the stuff
20 that we try to teach in the classroom, and here we are
21 in the real-world setting of it. It's sitting on a
22 zero.

1 The two compare in glaring ways, and we almost
2 have the ability to look at what happens when that
3 added personal handoff that we like to think might
4 occur, because people do get support and do find it, or
5 they interact with it digitally, or socially, or
6 whatever, we can't make that assumption. Once we put
7 it over the counter, it's over the counter, and it's
8 available for widespread without a learned
9 intermediary, with no assumptions. So we have
10 something that mimics that, that we can actually look
11 at.

12 So I appreciate the work of the sponsor to
13 bring the studies to bear so that we can look at them.

14 DR. NEILL: Ms. Mack-Brooks?

15 MS. MACK-BROOKS: Thank you. I think in
16 evaluating the efficacy, like Dr. Nelson said earlier,
17 most consumers have the opportunity to discuss with
18 medical providers and/or their community counselors, if
19 you will, and other professionals. I believe that the
20 product is just another modality to help in their
21 behavioral choice if they want to quit smoking.

22 DR. NEILL: Dr. Hatsukami, and then

1 Dr. Zorich?

2 DR. HATSUKAMI: I think that everybody is
3 invested in terms of maximizing success. I guess I'm
4 not really quite sure whether having GSK, for example,
5 go back and do another clinical trial with the bells
6 and whistles -- the behavioral treatment support that
7 quit.com is going to offer, as well as the video that
8 shows them how to use the product -- whether it would
9 really alter the relative ratio of success; probably if
10 it's very similar to other products that are on the
11 market, which is between 1.5 to 2.0.

12 So I don't know if it will change that. I
13 think it might enhance the rates of success, but I'm
14 not sure whether it will change that. I guess what I'm
15 trying to say is that I'm not sure whether it's worth
16 the expense and the time to actually require that
17 another trial be conducted where they would include
18 some of the additional tools that could be used by the
19 consumers.

20 DR. NEILL: Thank you. Dr. Zorich?

21 DR. ZORICH: I want to join in that comment by
22 saying that unless I'm mistaken, Dr. Winchell, the

1 patches, lozenges, and gums were done with designs that
2 were more like study 11 than 38.

3 DR. WINCHELL: The original Rx approval?

4 DR. ZORICH: Not Rx; switches.

5 DR. WINCHELL: The switches were not like
6 study 11.

7 DR. ZORICH: Were they like study 38?

8 DR. WINCHELL: More or less. People came in.
9 There were some differences. People had to pay for the
10 product, so that was --

11 DR. ZORICH: Motivating.

12 DR. WINCHELL: -- one thing that would
13 potentially mitigate against people coming back. But
14 there was no behavioral counseling. There were some
15 self-help materials just to -- it was here's the
16 product; go forth and try to quit. And then they would
17 come back and --

18 DR. ZORICH: I would say in my experience,
19 because I did a lot of use trials, that people paying
20 for product actually is motivational because I had to
21 pay for it, so now I better use it. So I think it has
22 the opposite effect in my experience.

1 I think, to reflect on the comments that have
2 been made by Ruth and Dorothy, that if you look at
3 these two trials, I agree with you that I think the
4 company has provided 11 with some not very
5 impressive -- the amount of minutes spent with people
6 were like 3 to 10 minutes or so at the sites in terms
7 of encouragement and counseling, and then what I would
8 almost consider a worst-case scenario. "I'm going to
9 go buy it. I'm not even going to open the package for
10 whatever reason, appropriately. I'm not going to go to
11 the websites. I'm not going to get the app," and here
12 are the results.

13 So to me, I think what we could expect is once
14 a product like this was in the marketplace, that we
15 have an example of a worst case without any
16 intervention at all, and then hopefully people would
17 access the available tools, apps, websites, and it
18 would improve the results to be anticipated.

19 DR. NEILL: Thank you. So we're coming up on
20 3:00. We've got Dr. Roumie's hand and Dr. Michele.

21 Dr. Michele, did you have a comment
22 specifically about this?

1 DR. MICHELE: Yes. I just wanted to clarify
2 over-the-counter conditions of approval, which is when
3 we approve a product over the counter, we approve it
4 based on the conditions of the clinical trial in terms
5 of what is required. So the stuff that you see in this
6 package, which is what was provided to people in the
7 clinical trial, is what would be approved. All of
8 these other things that GSK is talking about,
9 unfortunately, they are good corporate citizens who
10 want to help people quit and provide these things, they
11 would not be required to do so. That would not be a
12 condition of approval because they didn't test it that
13 way.

14 So whatever the company chooses to put out in
15 that setting would be entirely at the discretion of the
16 company, whereas what is approved in the package is
17 therefore required. So if a product were to then have
18 a generic come out, the generic would be based on the
19 conditions of approval. And again, it would be at the
20 company's discretion as to what other self-help aids
21 they provide or do not provide.

22 DR. NEILL: Dr. Roumie?

1 DR. ROUMIE: My comment was very much related
2 to that. And to Dr. Hatsukami, I think that it becomes
3 a safety issue for over-the-counter use if the
4 directions are unclear. So I don't know that the data
5 that we saw, that was based in the drug label
6 comprehension, really clarified to people how to use
7 the drug appropriately to then quit.

8 So to me, I think the additional work that may
9 be needed would be a clear label with more step-by-step
10 instructions on how to taper rather than you should use
11 about half of what you did start with; so something a
12 little more concrete based on the data that's already
13 come in, and then a more clear tapering schedule
14 because that kind of "lose, oh, about half, and then
15 you should be at about 4 by the end of 12 weeks," can
16 create a lot of confusion I think for your average
17 patient that's just reading the back of the box.

18 DR. NEILL: Thank you. So I'm going to wrap
19 up this discussion, because we're going to take a
20 break, and suggest that if there are additional
21 elements, themes that have arisen, that you feel might
22 be related to label comprehension, at the return of the

1 break, we're going to discuss that. But we will, as
2 well, have the opportunity, after you vote on question
3 3, to explain your vote, yes or no, regarding efficacy.

4 So with that, we will now take a 15-minute
5 break. Panel members, remember, there should be no
6 discussion of the meeting topic amongst yourselves or
7 with any member of the audience. We will resume at
8 3:15.

9 (Whereupon, at 3:00 p.m., a recess was taken.)

10 DR. NEILL: The sponsor has asked, and I have
11 agreed, to allow them to make one comment about
12 question 1, which I think we have discussed thoroughly.
13 This is specifically about the issue of the nicotine
14 replacement gum and some of the early studies done in
15 support.

16 Raj?

17 DR. MISHRA: Actually, it's the lozenge trial.
18 I'll just invite Dr. Nides --

19 DR. NEILL: Oh.

20 DR. MISHRA: -- to just quickly clarify that.
21 Thank you.

22 DR. NEILL: Very good.

1 DR. NIDES: Mitchell Nides, Los Angeles
2 clinical trials. I just wanted to make a
3 clarification, if it is in fact correct, that the only
4 other direct OTC product, I believe, is the nicotine
5 lozenge. The others were switch studies. The nicotine
6 lozenge study, as we showed in the comparison, was much
7 more similar to the 11 study. It had much more
8 counseling than the 11 study did. It had a week of
9 preparation before the quit day.

10 They excluded people as they went along if
11 they weren't quit, which was a tremendous motivator,
12 not only to the subjects in the study, because they
13 were getting some subject fee, but to the investigator
14 sites, which I think partly has to do with the 30
15 percent placebo rate that was seen in that study. That
16 is a very, very high placebo rate.

17 There were many motivations in that study for
18 people to get quit and stay quit through the continuous
19 abstinence period. That was not at all like the 38
20 study that was done, which was naturalistic. We had no
21 support, all the things we've talked about before. We
22 saw the same doubling of the quit rate. You may think

1 that it's low, but you take the two of them together,
2 and you're seeing probably more of what it's going to
3 be like in the, quote/unquote, "real world and real
4 life."

5 So I just wanted to make that clarification in
6 terms of what study 38 was in comparison to the
7 lozenge.

8 DR. NEILL: Thank you.

9 DR. MISHRA: Thank you for the opportunity.
10 Thank you.

11 DR. NEILL: So we're going to move to
12 question 2. Discuss the results of the label
13 comprehension study and their implications for efficacy
14 in the OTC consumer setting. We have already had some
15 discussion of the label in question 1, and I would
16 encourage if you have a distillation of that thinking,
17 or specific concerns, or specific recommendations about
18 the label, now would be the time to bring those
19 forward.

20 Dr. Parker, I know you're on the list. I
21 don't know if you want to be higher.

22 DR. PARKER: I'll put mine out there. I have

1 my list already on here, so I'll just list the ones
2 that I had noted. There's inadequate comprehension of
3 all steps. It's a multi-step set of instructions, and
4 there's not adequate comprehension of all the steps
5 that are involved demonstrated, based on the current
6 label.

7 I feel like it is an area that would need
8 further -- I'm concerned about the lack of an
9 assessment, nicotine being the active ingredient, and I
10 would think -- and I say this as a clinician -- I would
11 want my patients, and patients as consumers, to be
12 aware and to know that they're actually using nicotine
13 and also getting nicotine from whatever type of device
14 they get it from that is delivering it, and to be aware
15 that they're getting more of it.

16 I think the instructions regarding
17 stopping -- and also if you happen to quit smoking, you
18 don't need to finish all 12 steps maybe. I don't know
19 about that, but the exposure to something that is a
20 drug, that is a medication, that does have
21 pharmacologic impact, is not adequately communicated
22 nor tested in the label comprehension. So I have

1 concerns about that, especially in light of the
2 potential for misuse and abuse of nicotine itself as a
3 medication.

4 I think there has been a noble effort to try
5 to explain something that is incredibly complicated,
6 and you had to go down to a really small font to get
7 all the steps on it. But I think this is really
8 difficult to follow and to do, and without either -- or
9 you can call it shoe leather. You can call it a warm
10 handoff. I don't know about the support that you would
11 get technologically and how that would impact your
12 ability to follow it and use it, but I think doing this
13 by yourself for the average American is a task that is
14 beyond the reach of most.

15 DR. NEILL: So I gather if those type
16 recommendations were taken under consideration, your
17 belief is that the efficacy would improve.

18 DR. PARKER: I don't know that. I would have
19 to look for it to see. I wouldn't make that
20 assumption.

21 DR. NEILL: Okay. Dr. Farber?

22 DR. FARBER? Neil Farber, San Diego. I'm a

1 general internist and there are one of the many old
2 adages we do. And that is, if you have somebody who,
3 for example, has hypertension, you don't start two
4 drugs at the same time. You do one and see what
5 happens, and then do another if you need to.
6 Similarly, if you're trying to get somebody off
7 medications, you do one, see what happens, and then do
8 another one.

9 I understand the idea about the immediate
10 spray and the idea that people are getting much more
11 prominent relief in a quicker way, but that's parried
12 with we're going to let you do it the way you want.
13 And the problem with that is it's very confusing. It
14 leaves people very open to not knowing exactly what
15 they should be doing, and I have real concerns that it
16 was done in that way.

17 I think that patients will need more guidance.
18 I think that's clearly shown by the label comprehension
19 study, where if you add all three together, it was less
20 than 50 percent, even in those who were not literacy
21 challenged. So my recommendation would be to either
22 make the label instructions much more clear as to what

1 to do or maybe even not make the product be one in
2 which people can choose to do as they wish, but rather
3 give some guidance.

4 DR. NEILL: I'm going to play devil's advocate
5 for a bit. I was raised in Kentucky, where it was not
6 difficult to get work cutting and sticking tobacco in
7 the summer. And if you weren't careful, you got green
8 tobacco sickness, which everybody knows puts you off.
9 It's nicotine poisoning. And I as a physician have
10 seen patients and teenagers who decided to be cool, and
11 they smoke a couple of cigarettes until they puke, and
12 they realize that's not much fun.

13 My sense is that in terms of the implications
14 of being able to use the label, it either won't be
15 effective because people aren't getting the proper
16 dose, or they're going to make themselves sick; not
17 kill them, not cause other serious adverse events, but
18 turn them off the product. And I realize that that's a
19 risk, but my sense is that that is within a market
20 milieu in which they have a choice of lozenge versus
21 this. And if there's an advantage or a distinction, it
22 seems that it's the pharmacokinetic profile. These are

1 people who are looking for a hit, like literally, and
2 the pharmacokinetic data seems to suggest that if used
3 as directed, they will get that; not like they would
4 with a cigarette, but they will get that.

5 So I'm hearing the concerns about label
6 comprehension. I can barely read the size of this, and
7 yet I'm challenged when I consider the implication of
8 that for its efficacy in the real-world setting, to
9 imagine that it can do anything other than improve quit
10 rate, however marginally, or fail. And failure is the
11 expectation. I mean, if you haven't failed, you
12 haven't tried. Go fail. Go. Get on it. Prove it.

13 Dr. Pruchnicki, I saw your hand and I saw
14 several others, and Ms. Mack.

15 DR. PRUCHNICKI: Maria Pruchnicki. I guess I
16 just wanted to restate that I do think with the current
17 packaging, it's incredibly difficult for patients to
18 have any chance to accurately assess their own use
19 without some sort of a counter. I imagine that they
20 could keep track maybe up to 10, or 12, or 20 uses
21 during the day, and maybe that's the most typical. But
22 beyond that, I know there's probably no way in my daily

1 life I could spend that much time tracking something.

2 So I do think that that would be an
3 improvement if there was some way to track use a little
4 bit more related to the device itself. And the other
5 thing I just want to say, probably just yet again, is
6 just that step 2 is very vague, and it requires that
7 they have some of that baseline awareness of how much
8 they're using, and be able to do a rather complicated
9 step of thinking about what's half at week 9.

10 Most patients, I think that does not help them
11 be successful with the product. Although, maybe
12 failure is the expectation, I don't think we want to
13 frustrate patients unnecessarily as they try to do
14 something that literally lifesaving.

15 DR. NEILL: Ms. Mack-Brooks?

16 MS. MACK-BROOKS: Pamela Mack-Brooks. I was
17 going to say, just thinking about the patient with low
18 literacy level that won't read this., they get
19 help -- most patients, I think with low literacy that I
20 have experienced, after they may try and not be so
21 successful in doing it themselves, ask. We have
22 professionals, pharmacists, nurses, certified health

1 education specialists, that would go out of their way
2 to work on a project like this, to help those with low
3 literacy level comprehend, to make a schedule, to
4 figure out how to mark.

5 I think we just have to trust that even the
6 students of medicine and all the previously listed
7 professions would be willing to work, if this product
8 is approved, with sponsor or ambassadors of the product
9 in the retail market to make it work for those who need
10 it. I think the motivation is this is another way and
11 another modality for those who may have not been
12 successful with other ways. That's it.

13 DR. NEILL: Thank you. Dr. Krishnan-Sarin?

14 DR. KRISHNAN-SARIN: What I would like to say
15 about that is why definitely the expectation might be
16 failure, the point is people will also get put off by
17 the fact that this medication did not work for them.
18 And even if they wanted to try to quit again, they may
19 choose not to go with this.

20 So I think it's to the company's advantage to
21 provide them appropriate guidance of how to use it so
22 they are successful with this. So that would be the

1 argument I would put forth for saying the label does
2 need to be better and the guidance does need to be
3 better.

4 DR. NEILL: Do you have any specific
5 suggestions --

6 DR. KRISHNAN-SARIN: I definitely think --

7 DR. NEILL: -- not considering the font
8 size --

9 DR. KRISHNAN-SARIN: -- everything everybody
10 has been saying, like the stage 2, the stage 3, the
11 switching from one to the other, the instructions could
12 be improved.

13 DR. NEILL: Thank you. Other discussion
14 points? Dorothy?

15 DR. HATSUKAMI: Dorothy Hatsukami. I guess
16 with regards to step 1, where they're informed or
17 instructed to use when they have a craving or a
18 situation in which they may have a craving, I think
19 it's a really step forward, actually, because it's
20 really, addressing the smoker where they're at. I've
21 always thought it was really important to think about
22 using a medicinal product when they actually need it

1 instead of every 2 hours or every hours.

2 So I think it's a good step. I don't think
3 it's really that difficult for people to understand,
4 and smokers to understand, to use it when they're
5 feeling a craving or they have a craving. If it is
6 partnered with some kind of social behavioral
7 treatment, like monitoring the situations in which you
8 might want to smoke, then that would be an added
9 benefit because they will know, "Well, maybe I need to
10 take a few sprays before I go to the bar, where my
11 smoking is --" I guess nowadays there are smoke-free
12 bars, so I guess -- or when they drink, they know to
13 take a couple of sprays. So I don't think that's a
14 negative in terms of instructions provided to smokers.

15 I think actually getting people to use the
16 product is more of a challenge than having them use too
17 much of a product. So having them use a counter or
18 some way to systematically try to monitor how much
19 they're using a product, I don't know if that in the
20 long run, that's going to have a major benefit. I
21 think it's just another impediment, another step that
22 people need to take.

1 Again, I think the whole issue is underdosing
2 rather than overdosing with the medicinal products, so
3 I'm not really sure whether that will add that much to
4 influencing the efficacy of a particular product.

5 DR. NEILL: You know, this issue of the
6 counter has come up a couple of times, and I've asked
7 the question, how do you know whether it's empty? And
8 I honestly don't know whether a counter or having a way
9 to test would improve quit rates. And I contemplate
10 the methadone phenomenon, where people are given blind
11 doses that change without regard.

12 Also, my early experiences as a prescriber of
13 Nicotrol, inhaled nicotine, using an inhaler, that I'm
14 confident I still have a patient who 20 years later has
15 the same empty inhaler, but it's kind of a ritual thing
16 she does.

17 (Laughter.)

18 DR. NEILL: And I wonder if we're going to see
19 people carrying these around and just spraying. Of
20 course, I haven't asked, and I'm not asking, when it's
21 empty, does anything spray? I don't want to know. But
22 I think that those types of considerations inform the

1 ambiguity of, hmm, what's going to happen to actual
2 quit rate and cessation because we're all individual in
3 how we approach our habit and our addictions.

4 DR. HATSUKAMI: To me, I could tell that it
5 was empty if you kind of shake it because you can feel
6 the fluid. So I think people would be able to detect
7 whether it was empty or not, but maybe there are some
8 that aren't very sensitive to that.

9 DR. NEILL: I'm imagining the patient that's
10 calling me at 2 in the morning --

11 DR. HATSUKAMI: And saying --

12 DR. NEILL: -- "I really need a cigarette.
13 I've got to have a drag. Is there something in it?" I
14 mean, they're going to test what they're going to
15 spray. They're going to do something. They will tell
16 us. They will have a definitive way to tell us whether
17 it's empty; I'm confident.

18 So I interrupted, but both Dr. Krinsky,
19 Dr. Di Francesco, and Dr. King have some comments as
20 well.

21 DR. KRINSKY: Hi. Dan Krinsky. I agree with
22 the comments that have been made so far about the lack

1 of comprehension for all three of the steps combined.
2 I think that's a concern. The idea of the counter to
3 me is interesting. It might provide users with more
4 immediate feedback if they see numbers on there as to
5 it was on this today, and it was on this yesterday, or
6 some gauge as to how much they're using. And maybe
7 they could even use more to help with their success.

8 Then as far as the package labeling is
9 concerned, there was concern about who opened the flap
10 to read more. And if there was more of a prompt on the
11 outside to read more, to learn more, to encourage that
12 opening of the flap to get better educated about the
13 potential use of the product before the purchase, I
14 think that might be helpful as well.

15 DR. NEILL: Dr. Di Francesco?

16 DR. DI FRANCESCO: Lorenzo Di Francesco,
17 Emory. One of the concerns I have with, obviously, the
18 data from the label comprehension study is that clearly
19 people had trouble understanding a multi-step process,
20 and since the vast majority of people may get to the
21 end of the 12 weeks and actually have not quit, and the
22 guidance in the packet says you're 12 weeks, and you're

1 still using, go talk to your provider, I am concerned
2 about how hard it is to get into your provider, for
3 one, to try to get that guidance as to what to do next.

4 What is the person going to do between the 12
5 weeks and when they're trying to get into their
6 provider? How are they going to manage themselves?
7 Are they just going to fail and get back to the
8 cigarettes because they've done the 12-week trial? And
9 whether there's some guidance there that can be given
10 to the patients because the vast majority of these
11 patients are going to fail, and that would be helpful I
12 think in the big picture.

13 DR. NEILL: Dr. King?

14 DR. KING: Tonya King. This is just a
15 comment. This may not be the area that we're focusing
16 on today. But I noticed that there are 140 sprays in
17 one, and if they are really using up to 64 a day, this
18 is only going to last a little over 2 days. So I don't
19 know what the cost is involved, but just something to
20 consider.

21 DR. NEILL: Thank you. Seeing no other hands,
22 and realizing this is discussion, I'm going to look to

1 FDA. Were there specific elements of this question
2 that you feel we haven't touched on?

3 DR. MICHELE: I think you've covered it.
4 Thank you.

5 DR. NEILL: You're welcome.

6 Let's move to question 3, Our first voting
7 question. Do the data provide substantial evidence of
8 efficacy of nicotine mouth spray as a smoking cessation
9 aid in the OTC setting?

10 Let me remind you, we're going to be using an
11 electronic voting system when we vote. And as a point
12 of process, let me point out I am not intending that we
13 as a committee re-discuss this question, which is
14 similar enough to me to number 1. If you have
15 questions specifically about the wording, I'd be happy
16 to entertain them. But otherwise, what I'm going to
17 propose is that we vote, and then once voted, we'll go
18 around the table -- Dr. Zorich, you're
19 nonvoting -- from Dr. Krishnan-Sarin, around to explain
20 your vote if you wish to.

21 So a clarifying question, Dr. Curry?

22 DR. CURRY: The word "substantial," can

1 somebody tell me what that means?

2 DR. NEILL: FDA?

3 DR. MICHELE: I think I tried to provide this
4 as part of the background when I read the regs, but
5 basically I'm going to go back one moment to the reg
6 and pull this up so that I give you the exact language.

7 "Substantial evidence consisting of adequate
8 and well controlled investigations," which is plural.
9 So generally speaking, you need more than one. In
10 essence, we consider "substantial evidence" to mean
11 that efficacy must be certain and without any doubt.
12 That's why we generally asked for two studies, and the
13 statisticians in the room can tell you that if you have
14 a p-value of 0.05, that means that 5 percent of the
15 time you're getting it wrong and you're showing a
16 benefit when in fact there is none. And if you combine
17 two studies that both show that, then your chance of
18 getting it wrong goes way down.

19 That is what we're trying to do here. We want
20 to make sure that we are approving beneficial therapies
21 that also have an appropriate safety side, and we're
22 always struggling with that benefit-to-risk ratio

1 because everything that we're talking about is a drug,
2 so no drug is a hundred percent safe. No drug is a
3 hundred percent effective; so just for your
4 consideration.

5 DR. NEILL: Thank you.

6 Yes, Dr. Krishnan?

7 DR. KRISHNAN-SARIN: How do we take into
8 consideration the discussion around point 2 in making
9 the decision about point 1, the label comprehension
10 issue? How do we take that into consideration when we
11 are looking at this decision?

12 DR. NEILL: However you vote, you're going to
13 have the opportunity, if you wish, to explain your
14 vote. If your concerns about efficacy, that perhaps
15 prompt you to vote no, arise because of concerns about
16 label comprehension, I would expect, given
17 sub-question A, for you to say we should have further
18 data about a new and improved label, based on improved
19 or refinement of steps, bigger fonts, suggestions.

20 I'm not sure. That's just an example. You
21 may also decline to provide. But however the vote
22 comes out, I want to reiterate what staff said earlier,

1 which is that the explanation of the votes can be
2 helpful as well, which is why we'll ask folk if you
3 have a new or different rationale for voting the way
4 you did, to please comment.

5 Yea?

6 DR. WINCHELL: If I could just clarify, maybe
7 this will help. This is the product exactly as it is,
8 yes or no, and any improvements that you think could be
9 made would be that those would not be this product.
10 That's a hypothetical that we could then consider.

11 DR. NEILL: So let me read the question again.
12 Do the data provide substantial evidence of efficacy of
13 nicotine mouth spray, 1 milligram per spray, as a
14 smoking cessation aid in the OTC setting? If no, what
15 further data should be obtained?

16 If there is no further discussion on this
17 question, we'll begin the voting process. Please press
18 the button on your microphone that corresponds to your
19 vote. You will have approximately 20 seconds to vote.
20 Press the button firmly. After you've made your
21 selection, the light may continue to flash. If you're
22 unsure of your vote or you wish to change, press the

1 corresponding button again before the vote is closed.

2 (Voting.)

3 LCDR CHEE: For question 3, we have 8 yeses,
4 7 noes, and zero abstain.

5 DR. NEILL: Everyone has voted, and the vote
6 is now complete. Now that it is complete, we'll go
7 around the table and have everyone who voted state
8 their name, their vote, and if you want to, you can
9 state the reason why you voted as you did into the
10 record.

11 Dr. Krishnan-Sarin, let's begin with you.

12 DR. KRISHNAN-SARIN: I voted yes. I think the
13 evidence does suggest that the mouth spray can be
14 helpful to smokers. However, I would like to add that
15 I would like to see some changes in the labeling to
16 make it more clearer to smokers, especially in the
17 transition from stage 1 to stage 2 and stage 3. It
18 needs to be much clearer and more guidance needs to be
19 provided.

20 DR. NEILL: Thank you. Dr. Curry?

21 DR. CURRY: I also voted yes. I think there
22 are two adequate studies, which meets the criteria that

1 we heard. I have a decade of experience on the
2 preventive services task force, and we always talk
3 about the magnitude and certainty, and I have
4 sufficient certainty of at least a moderate to small
5 effect that makes me comfortable with a yes vote on the
6 efficacy.

7 DR. NEILL: Thank you. Dr. Shoben?

8 DR. SHO BEN: Abby Shoben. I voted yes. Gosh.
9 I went back and forth with this several times over the
10 course of the day today. I'm thinking the final
11 analysis for me, it was confidence in this small effect
12 under real-world, potentially worst-case kind of
13 scenario, this 2 and a half point difference, which
14 does lead to a high number needed to treat, but we're
15 talking about something that's quite serious in terms
16 of smoking cessation.

17 So if you have to treat 40 people to get one
18 of them to quit, that is still efficacy in my mind.
19 And the data were consistent with other products done
20 in more similar types of settings, so that was how I
21 interpreted that. So I have confidence that this is
22 behaving relatively similarly to existing NRT.

1 DR. NEILL: Thank you. Dr. Nelson?

2 DR. NELSON: Dr. Nelson, Georgetown. I agree
3 with that. I think that, again, while the number to
4 treat is relatively high at 40, given the number of
5 people affected, there really is quite a few people
6 that you're potentially helping with is. I think it's
7 a close call because of the study, the efficacy. The
8 effect size is relatively small. I think there's
9 enough there that it's shown its efficacy.

10 DR. NEILL: Thank you. Ms. Thomas?

11 MS. THOMAS: Jill Thomas, patient
12 representative. I voted yes. I believe if I were
13 still smoking today, I'd probably would try this. I'm
14 not sure if it would help me, but it would definitely
15 be worth a try. I feel like if I was confused with how
16 to use it, I would probably just try something else.

17 DR. NEILL: Thank you. Ms. Mack-Brooks?

18 MS. MACK-BROOKS: Pamela Mack-Brooks. I voted
19 yes. I felt that based on the FDA definition, the
20 evidence was adequate, and based on other uses, I think
21 it's a good opportunity for another modality. Thank
22 you.

1 DR. NEILL: Thank you. Dr. Farber?

2 DR. FARBER: Neil Farber, UC San Diego. I
3 voted no. I think it's a good product. I think it has
4 a lot of potential, but I think it's just not yet ready
5 for prime time. I think it needs some work in terms of
6 labeling and in studies looking at whether the labeling
7 makes a -- improved labeling hopefully makes a
8 difference with either focus groups or re-do a study.
9 I'd also like to see a study comparing this head to
10 head in a blinded noninferiority trial with some of the
11 other nicotine replacement treatment.

12 DR. NEILL: Thank you. Dr. Krinsky?

13 DR. KRINSKY: Dan Krinsky. I also voted no, a
14 lot of the same reasons that Dr. Farber just mentioned,
15 concerns about labeling and just trying to get that
16 better optimized for the patients and the users. I
17 agree with Dr. Farber's suggestions about some of the
18 additional studies that we could do to truly get a
19 better handle on where this fits in with the other NRT
20 products that are available.

21 DR. NEILL: Thank you. Dr. King?

22 DR. KING: Tonya King. I voted no. I feel

1 like study 38 was really the true assessment of the
2 effectiveness in the over-the-counter situation. I
3 think that study 11, while it showed quit rates close
4 to what would be acceptable for a transition from
5 prescription, was conducted in Europe. We're talking
6 about approval for use here in the U.S., and that study
7 wasn't conducted here. So I think while there could be
8 promise in the treatment, I think it needs to be shown
9 that it's efficacious here in a different type of
10 study. Thank you.

11 DR. NEILL: Thank you. It's Richard Neill. I
12 voted yes. I practice in New Zealand right next to our
13 smoking cessation coordinator, who had this among many
14 other NRT tools in her panoply. I believe that the
15 state-based tobacco settlement smoking cessation, the
16 insurance-based tobacco cessation programs, the QuitNow
17 lines, the school, and all the other things hold small
18 but present hope that having another tool like this in
19 the armamentarium for patient or provider would allow
20 them to finally quit.

21 Dr. Di Francesco?

22 DR. DI FRANCESCO: Lorenzo Di Francesco. I

1 voted no, and it was predominantly -- I grappled with
2 this quite a bit because of the statistical
3 significance of the two studies, but it came down to
4 study 38, just having trouble seeing the results so off
5 kilter with some of the other studies that have been
6 done with the placebo rate being so low, and then
7 ultimately the treatment being low, that I just didn't
8 feel comfortable saying that there was substantial
9 evidence of efficacy.

10 DR. NEILL: Thank you. Dr. Pruchnicki?

11 DR. PRUCHNICKI: Maria Pruchnicki. I voted
12 no. This was also a very challenging question for me
13 to answer personally. I am one of those folks who
14 would love to have another tool when I'm working with
15 patients for smoking cessation, but I'm not sure that I
16 would have absolute confidence in this one at this
17 point because I do think study 38 causes some pause in
18 terms of, really, how can patients utilize this with
19 some of the directions and challenges with adherence.

20 DR. NEILL: Thank you. Dr. Roumie?

21 DR. ROUMIE: Christianne Roumie. I voted no,
22 and predominantly it was based on the efficacy standard

1 in slide 5, which said, "under the conditions suggested
2 in the proposed labeling." So my biggest issue is
3 actually with the proposed labeling, which is unclear,
4 as far as OTC standards. And we would never, for
5 over-the-counter drugs, say, well, take some, up to
6 this many per day and reduce it by half if you're
7 starting to feel better.

8 So I think patients need a little more
9 direction. And if the sponsor wants to maintain that
10 flexibility, I think that's great; then you really
11 should add testing of patient numeracy as far as the
12 revised drug facts label, if you want to be able to not
13 just understand if patients can understand the
14 directions as far as their health literacy, but this
15 requires numerical tasks for them, including counting
16 of doses and decrease of doses. So some sort of
17 assessment of that would be added benefit.

18 DR. NEILL: Thank you. Dr. Parker?

19 DR. PARKER: I voted no. I think most my
20 thinking was aligned with that of the others who voted
21 the same way. I went very specifically with the FDA
22 substantial evidence, consisting of adequate and

1 well-controlled investigations. And to my mind, we
2 only have one, and that would be 38 because 11 really
3 does not mimic the OTC setting, and that's the issue on
4 the table, in my mind.

5 DR. NEILL: Thank you. Dr. Hatsukami?

6 DR. HATSUKAMI: Yes. I voted yes. In large
7 part, it's because I think that there was demonstrated
8 efficacy of the trial. Number 38 did demonstrate
9 efficacy. I think it's pretty similar to the efficacy
10 that's been demonstrated in other naturalistic studies
11 involving over-the-counter nicotine replacement
12 products, and they're out in the market.

13 I also think that -- well, I wasn't as
14 concerned about the instructions, in large part because
15 we're talking about relative risk of a medicinal
16 product compared to smoking. And smoking certainly has
17 far more negative consequences associated than a
18 medicinal product that would contain nicotine, so I
19 wasn't as concerned about the labeling.

20 DR. NEILL: Thank you. That concludes the
21 vote and the discussion for those questions. The next
22 question is a discussion, number 4. Discuss the safety

1 of nicotine mouth spray, 1 milligram per spray, as a
2 smoking cessation aid in the OTC setting.

3 I will kick this off by suggesting that its
4 safety is established. It has a reasonably wide
5 therapeutic window, and while its efficacy we've
6 discussed quite a bit, I don't have concerns about its
7 safety.

8 We're going to start with Dr. Farber.

9 DR. FARBER: Neil Farber, UC San Diego. I
10 guess the one concern I have -- I think my concerns
11 about the concurrent use of the nicotine mouth spray,
12 along with smoking, have been somewhat allayed. But my
13 concern is regarding the increasing rise of vaping and
14 what effect that has not only if there's concurrent use
15 of vaping and smoking cessation tools at the same time,
16 but also are some people going to be thinking of a
17 quick shot inhaler the same kind of thing as vaping or
18 a cigarette in terms of getting that immediate kick,
19 and is that going to be a problem.

20 Thank you for that shoving.

21 DR. NEILL: Thank you. Dr. Shoben?

22 DR. SHOBEN: I wanted to say I mostly agree

1 with you, Dr. Neill, which is to say I really don't
2 have significant concerns about the safety of this
3 product, in part because it's been so extensively used
4 in other countries in similar settings, the numbers
5 that the sponsor gave about how many units have been
6 dispensed, and we haven't seen any kind of significant
7 safety signal the way that we have with e-cigarettes
8 and things like that. And these are countries where
9 e-cigarettes are definitely a similar level problem to
10 what's been in the U.S. as far as I can tell. So I
11 don't have significant concerns about this becoming a
12 new e-cigarette type problem here.

13 DR. NEILL: Thank you. Any other questions?
14 Dr. Parker?

15 DR. PARKER: I do have concerns about safety,
16 so I'll start with that. Dependence was the most
17 commonly reported adverse event, both in the FAERS and
18 the VigiBase, where the numbers were reviewed. Just
19 from a logic standpoint, this whole thing about -- I
20 don't think anybody wants to be nicotine addicted, but
21 you end up nicotine addicted. So if you're nicotine
22 addicted, it comes down to the question of do you want

1 to be nicotine addicted to this form or to another
2 form?

3 I don't know if it really -- nicotine is a
4 medication, and it has --

5 FEMALE VOICE: Or both.

6 DR. PARKER: -- or both. Okay, my friend
7 here. We're behaving, though, just so you know. So I
8 have concerns just thinking about it. Nicotine has
9 pharmacologic impact. We didn't do an extensive
10 discussion about that because we are always saying
11 compared to smoking cigarettes where we have data on
12 the negative consequences of cigarette smoking, but
13 nicotine addiction is not a desirable outcome of
14 anything.

15 So the idea of using nicotine with the
16 potential of -- I mean, when you see signals, we're to
17 look at FAERS and these databases only as -- they're
18 tips of icebergs. There are signals there, not cause
19 and effect, with all its limitations. But you also see
20 them, and you don't ignore them, and there's
21 significant data that's captured there.

22 So the issue of dependence to me is of

1 concern, and I see it as a safety concern, the
2 potential for nicotine dependence with this. And I
3 have concerns about making it available over the
4 counter. Even though it says age 18, no guarantees
5 whatsoever. You can already get it on the internet
6 right now, at eBay and other sources. So what does
7 that mean and is it something you want to see? I have
8 concerns about the potential for dependence, and
9 misuse.

10 DR. NEILL: Dr. Hatsukami?

11 DR. HATSUKAMI: I guess I don't have as much
12 concern about the dependence issue. It seems like the
13 nicotine mouth spray is pretty similar in terms of the
14 possibility of becoming dependent compared to other
15 over-the-counter products like nicotine gum and a
16 nicotine lozenge. If you were to choose between
17 cigarettes and using a product like this over a longer
18 period of time, certainly it would be less harmful to
19 use a product like this instead of cigarettes.

20 In terms of the long-term effects of nicotine,
21 it's hard to say -- we have to think about the snus
22 experience we were talking about before in Sweden.

1 What you see is you do see a dramatic decrease in terms
2 of cancer. You don't see cardiovascular risks increase
3 other than fatal myocardial infarction with the use of
4 snus. You do see dependence, as you had noted, so you
5 do see repeated use over time.

6 Certainly, you don't see respiratory problems,
7 which I don't envision that this would have primarily
8 because it is an oral buccal absorption rather than
9 inhalation. So when you take a look at relative risks,
10 I wouldn't be as concerned about becoming dependent on
11 this as compared to continuing to smoke cigarettes.

12 DR. NEILL: Thank you. Dr. Farber?

13 DR. FARBER: Neil Farber, UC San Diego. In
14 answer to that question, you said you don't see
15 anything in terms of adverse events except fatal
16 myocardial infarction. I think we want to avoid fatal
17 myocardial infarction as well.

18 The other thing I was thinking of when
19 Dr. Parker was talking was one of the things that I
20 noted, in looking at the manufacturer's slides on
21 serious adverse events, the second one that's listed is
22 incorrect drug administration duration. I wonder if

1 that's not so because of the kick and/or addiction that
2 is occurring. Even if it's not described as drug
3 dependence, it's basically the equivalent thereof. So
4 I think that is somewhat of a concern.

5 DR. NEILL: Dr. Hatsukami?

6 DR. HATSUKAMI: I wanted to clarify. It's
7 among those people that have cardiovascular disease
8 that they experience. So even though there's not an
9 increased risk of cardiovascular disease among those
10 who are snus users, it's among those individuals that
11 might have an increased incidence of fatal myocardial
12 infarction. That is a negative, but it's not as though
13 they're at increased risk compared to those who aren't
14 using snus products, if you understand what I mean.

15 DR. FARBER: I think what you're seeing is
16 they're not at an increased risk of de novo
17 cardiovascular disease, but if someone who has
18 cardiovascular disease uses the product --

19 DR. HATSUKAMI: There's a higher probability.

20 DR. FARBER: -- there is a higher probability
21 of them having a myocardial infarction.

22 DR. HATSUKAMI: Right, right. Exactly.

1 DR. NEILL: Thank you. Dr. Curry?

2 DR. CURRY: I'm just reminding myself that the
3 last conversation was about snus and not about this
4 product.

5 I actually came to this meeting really
6 concerned about the safety of this product, and
7 concerned in the context of what's happening with
8 vaping. I asked all the questions that I needed to ask
9 about it, and I felt satisfied by the answers that I
10 got, so I don't have serious concerns about the safety
11 at this point.

12 DR. NEILL: Thank you.

13 Seeing no other hands, I'm going to look to
14 staff. Were there other specific concerns or themes
15 within the area of safety that you wish the panel to
16 address?

17 DR. WINCHELL: I was going to offer the
18 services of our dental consultant, but I think he
19 escaped, if people had questions about the visual mouth
20 inspection results, but I can't. If people did have
21 specific questions about that, the medical reviewer who
22 worked with the dental consultant might be able to

1 answer them.

2 DR. PARKER: I would love to hear those. I
3 wondered -- can you speak to them or we need to wait?

4 DR. WINCHELL: If you let us know what your
5 questions are, we may be able to field them. We're
6 familiar with what the dental team found.

7 DR. FARBER: I'm sorry to interrupt.

8 DR. NEILL: Go ahead, Dr. Farber.

9 DR. FARBER: Neil Farber, UC San Diego. The
10 thing I'd be interested in is knowing if there's any
11 specific data among people vaping, in terms of safety
12 issues, given the increasing numbers.

13 DR. NEILL: Go ahead, Raj.

14 DR. MISHRA: Obviously, we don't have any data
15 on people who are vaping and using this product. So we
16 don't have any specific data on that.

17 DR. NEILL: I'm going to defer the question
18 about the dental inspection until it comes in. I will
19 refresh my memory, a bit, that when that data was
20 presented, this was over the relatively short term of
21 the study, and there were small but present changes
22 that were seen. These were different versus placebo,

1 but I did not hear data about versus other oral NRT
2 gum, lozenges, et cetera.

3 Maybe I should ask staff generally, are you
4 familiar with data that suggests this would be
5 differentially cause for concern versus other NRT
6 dosage forms?

7 DR. MICHELE: One thing that's a little bit
8 different about this one is that you are spraying
9 directly on to the oral mucosa, so the full effect of
10 the dose right there locally is occurring as opposed to
11 with some of the other oral dosage forms. You're kind
12 of moving it around. You're not parking it in the same
13 spot the whole time, for example, with the gum.

14 So that was just one of the items that was
15 raised by our dental folks. I don't want to go too
16 much further on that space since they should speak for
17 themselves.

18 DR. NEILL: Dr. Krishnan?

19 DR. KRISHNAN-SARIN: I was just going to say,
20 I was not particularly concerned about this one, the
21 dental findings, because I believe that similar
22 findings have also been seen in smokers, too. So I

1 wasn't particularly concerned about it, and I just
2 wanted to add that from a health effect perspective,
3 just health effects, I don't have concerns.

4 DR. NEILL: Thank you. Dr. Pruchnicki?

5 DR. PRUCHNICKI: Maria Pruchnicki. I want to
6 say that I don't think as labeled, or even in the
7 situation of maybe excessive use for this product, that
8 I'm particularly concerned about safety, but we are
9 introducing a package into the marketplace that doesn't
10 exist in terms of a liquid formulation that's
11 available, at least when full, in a rather large dose.

12 I know with my students at Ohio State, we
13 spend time counseling patients about safe disposal of
14 patches and keeping things like that out of the reach
15 of children and pets who are, at least in my
16 experience, less discerning when it comes to the flavor
17 of something that they're willing to eat.

18 So that could be potentially a concern, and I
19 don't see anything on the product label about the fact
20 that it could be toxic in large quantities, or harmful
21 to children and pets, and maybe what to do in those
22 circumstances, which might just be an addition that we

1 need to consider.

2 DR. NEILL: Helpful. Thank you.

3 I'm going to suggest that we move on to
4 question 5. This is a discussion question. Discuss
5 the potential for abuse of nicotine mouth spray,
6 1 milligram per spray, by the adult and pediatric
7 populations in the OTC setting. Consider its
8 pharmacokinetic profile and other characteristics that
9 are different from currently marketed OTC nicotine
10 replacement therapy products.

11 Dr. Krishnan?

12 DR. KRISHNAN-SARIN: I have to start out by
13 saying that I am very concerned about the availability
14 of this product in the open market and it's use by
15 pediatric populations. When the e-cigarettes first
16 came out, I was one of the first people to raise this
17 as a concern, and I was really yelled at and told to
18 shut off, and I didn't. And now we are seeing what
19 happened with the e-cigarette epidemic so to speak.

20 This is a concern, and I think this can be
21 addressed. I think there are ways that a company can
22 get additional information, talking to kids, seeing if

1 this would be appealing to them. There could be work
2 that could be done to salvage this. I don't think that
3 it's going to -- I don't know how it's going to weigh
4 in my vote, but I am concerned about its use in
5 pediatric populations.

6 DR. NEILL: Thank you. Dr. Curry?

7 DR. CURRY: Sue Curry, for the record. I
8 finally said my name before I gave a comment. I
9 apologize. I would be concerned if I thought that GSK
10 would take a page from the tobacco industry playbook
11 and be advertising and encouraging youth to use this,
12 and I don't see any evidence of that.

13 I think you were prescient in the potential
14 for abuse with e-cigarettes, but it's in a very
15 different marketing climate, and regulatory setting,
16 and so on and so forth. Again, I had questions about
17 that, and I did feel like they were answered.

18 DR. NEILL: Dr. Sarin?

19 DR. KRISHNAN-SARIN: I'm sorry. Did you ask
20 me? I would have agreed with that if I did not know
21 how JUULs were advertised. The only advertising JUUL
22 ever did when it first came out on the market was one

1 social media posting that happened, and that was it,
2 and that took off in so many ways. Sherry Emery has
3 presented some of those data, looking at the results
4 and what JUUL actually posted. There wasn't that much.

5 These things have a tendency to take off as
6 far as youth are concerned, and it's important to
7 understand how youth will use this and also how we can
8 deter them from using it by placing appropriate
9 information on the label.

10 DR. NEILL: Thank you. Dr. Hatsukami?

11 DR. HATSUKAMI: I wasn't really going to say
12 much. Dorothy Hatsukami. I was just going to
13 reinforce what Dr. Curry was saying, is that they do
14 have a different marketing method than JUUL or any of
15 the electronic cigarettes. I'd imagine that they
16 aren't going to have the social media presence that
17 electronic cigarettes had. It's certainly a lot more
18 cooler and attractive to see smoke or smoke vapor
19 coming out of your mouth than just spraying into your
20 mouth.

21 I think cost might be an issue, too. The fact
22 that this is a medicinal product, costs might actually

1 reduce the profitability that youth would start
2 misusing or abusing this product.

3 DR. NEILL: Thank you. Dr. Di Francesco?

4 DR. DI FRANCESCO: Lorenzo Di Francesco,
5 Emory. I'm a little concerned about the abuse
6 potential in the adolescent population, particularly
7 because the vaping craze has a kind of coolness to it.
8 The devices are small, but they do run the issue
9 of -- kids are smoking around the legal system, and the
10 schools, that you really wonder about products that
11 don't have smoke that are a little bit more
12 surreptitiously able to be hidden and squirted.

13 I think you have to be careful of that as you
14 pitch this product forward that it doesn't become the
15 silent way that kids are going to abuse nicotine to get
16 around the system, as schools are now putting into
17 place detectors in the bathroom to catch people smoking
18 now and to try to control that epidemic.

19 DR. NEILL: Thank you. Dr. Krinsky?

20 DR. KRINSKY: Thank you. Dan Krinsky. I
21 agree with a lot of the comments that have been made so
22 far about the concerns with e-cigarettes and vaping,

1 and I think as we're going to see more regulation
2 around e-cigarettes and vaping, kids are going to look
3 for alternatives, and they're very creative. This is
4 something that they can easily disguise in their
5 pockets. So again, I don't think it's a huge concern,
6 but I think it's definitely a concern that we need to
7 think about.

8 DR. NEILL: Dr. Roumie?

9 DR. ROUMIE: I think, theoretically, just even
10 looking at the PD data from the sponsor and the mean
11 urge to smoke that they have on the Y axis, there's a
12 rapid reduction, and then it exceeds the -- your urge
13 to smoke actually surpasses in the mouth spray what you
14 have in the nicotine lozenge, 2 milligram and
15 4 milligram. Their own data shows that kind of quick
16 decline, and then you actually go much higher. And it
17 just concerns me that that pattern is one that we see
18 with drugs of abuse.

19 DR. NEILL: Thank you. Dr. Parker?

20 DR. PARKER: So I would say that the product
21 will be used by people less than 18. I would make that
22 assumption. I don't know how you could keep it from

1 getting on the internet right now if all you need is a
2 credit card to verify your age. I think that sort of
3 captures the ease with which its use will be
4 disseminated.

5 So I think the question of is this safe -- do
6 we want to just put it in the water? So I've got
7 questions about it because we've seen more than just a
8 little signal about the dependence that happens with
9 nicotine and the pharmacologic impact. If you've never
10 been a smoker, like me, and you chew a piece of gum,
11 look at how it makes you feel.

12 I think that's what we're looking at. So it's
13 do we want to put another product that becomes
14 available, that's known to have dependency and
15 addiction, available more readily than it currently is?

16 DR. NEILL: Dr. Nelson?

17 DR. NELSON: David Nelson. Do we have any
18 data from Europe, et cetera, on use in kids? Because
19 it's been used there for a while in a lot of countries.
20 I think that would be very informative and help answer
21 this question.

22 DR. NEILL: The sponsor rose quickly when you

1 asked that question, so I'm guessing that they do.

2 DR. MISHRA: From all of our postmarketing
3 experience, we have not had any reports of naive
4 individuals getting addicted to this product.

5 DR. NEILL: I'm sorry. I didn't catch the
6 first part. You've not had any evidence of --

7 DR. MISHRA: Those who are nicotine naive
8 using this product and then getting addicted to
9 nicotine; we haven't had any --

10 DR. NEILL: So no evidence of nicotine naive.
11 Thank you.

12 Dr. Hatsukami?

13 DR. HATSUKAMI: Dorothy Hatsukami. Just
14 harking back to what Dr. Parker had said, I think the
15 failings of our medicinal products right now is that it
16 doesn't have good abuse liability and can't compete
17 with cigarette smoking. That's one of the reasons why
18 we're not seeing a great success rate with that
19 product.

20 So I agree with you; we need to keep it out of
21 the hands of adolescents. that aren't using tobacco
22 products, so I think that that's important. But we

1 also need to keep in mind that these products are
2 intended to affect the adult smoker that is having
3 difficulty quitting. And in fact, I would go for a
4 higher abuse liability of a product to help them quit
5 smoking and have greater success rate than what this
6 product shows.

7 DR. NEILL: Thank you. So I think we've had
8 adequate discussion about this question. Before we
9 move to the next, question 6, a vote, I'm going to ask
10 staff whether our expert on the dental findings in
11 these studies has appeared.

12 I would be most interested, then, if you could
13 comment on differences, if any, between the safety data
14 seen in this NMS and other oral NRT.

15 DR. WINCHELL: I can predict that Dr. Kettl
16 will not be able to comment on that.

17 DR. NEILL: Oh, okay. Then I'm going to
18 withdraw that question, and we're going to move on.

19 So let's go to question 6. This is
20 about -- Ruth, you're giving me a look.

21 DR. PARKER: I wish I could find it quickly,
22 but I can't. But my memory was that -- is it VMI? I

1 didn't even know what it stood for until later after I
2 read it.

3 DR. WINCHELL: Visual mouth inspection.

4 DR. PARKER: Visual mouth inspection, VMI;
5 that the VMI did have dental findings in those who
6 began to use it. And I would like to know what those
7 are. I know there's some leukoplakia. I know there's
8 some ongoing stuff, but it seemed like this was
9 something where it would be really nice to know a
10 little bit more about what that was all about.

11 So I'd love to hear from the agency. If the
12 sponsor has something, that's fine, but I'd really like
13 to hear from the agency about their look at that.

14 DR. WINCHELL: Sure.

15 DR. PARKER: Is there a signal?

16 DR. WINCHELL: We do have somebody coming who
17 will address that. The dentist who reviewed the data
18 did do her own coding and analysis, so her numbers
19 might be a little different from the sponsor.

20 DR. NEILL: In the meantime, I'm going to move
21 us to question number 6. This is a voting question,
22 and as with the other, we're going to read the

1 question. I will ask for any clarifying questions
2 about this question. We'll answer those, and then
3 we'll vote and ask folk to go around and explain their
4 vote.

5 Having said that, I now hear from staff that
6 Dr. Kettl is here.

7 Hello, Dr. Kettl. Welcome.

8 DR. KETTL: Dr. Neill, thank you.

9 DR. NEILL: There are two issues. One is
10 about the signal present in the use of NMS and dental
11 findings, both the description of findings and their
12 magnitude.

13 DR. KETTL: I'm Dave Kettl. I'm The dental
14 team leader in the Division of Dermatology and Dental
15 Products. I think the short answer is there were
16 evidence of various pathologies at baseline, and there
17 was a small increase in that over the course of the
18 studies. The bottom line in interpreting that data I
19 think is that we don't have comparative data versus the
20 other nicotine products, nor can we really make any
21 valid assessment about the impact of continued smoking
22 versus the impact of the pharmacologic product that was

1 introduced to the mucosa.

2 DR. NEILL: Thank you.

3 So I've heard some of the opinions of the
4 committee specifically about that issue, suggesting
5 this may be small; others that this might be something
6 to look forward to. And we'll trust that the
7 discussion being read into the record will allow staff
8 to refer to that in their deliberations about moving
9 forward.

10 Is that fair, Dr. Michele?

11 DR. MICHELE: Yes. Thank you.

12 DR. NEILL: Great. Thanks, Dr. Kettl.

13 DR. KETTLE: Thank you.

14 DR. NEILL: So let's go to question 6. Do the
15 data provide substantial evidence of safety of OTC use
16 of nicotine mouth spray, 1 milligram per spray? If no,
17 what further data should be obtained? Are there any
18 clarifying questions about this? Dr. Krishnan?

19 DR. KRISHNAN-SARIN: So my question is similar
20 to the one I asked the first time. How do we take
21 number 5 into consideration when answering number 4?
22 Which is what the question is all about. The abuse

1 liability question was presented to us as a separate
2 question initially, but here now are we taking it into
3 consideration in safety?

4 DR. MICHELE: Yes. So when we consider the
5 safety of an over-the-counter drug, we also consider
6 the abuse potential of that product and misuse.

7 DR. NEILL: Are there any other clarifying
8 questions about this voting question?

9 (No response.)

10 DR. NEILL: Good. Seeing none, I would
11 encourage you to vote.

12 (Voting.)

13 LCDR CHEE: Question 6, we have 9 yeases,
14 6 noes, and zero abstain.

15 DR. NEILL: The vote is now complete, and
16 we're going to go around the table starting on this
17 side with Dr. Hatsukami. Please read your name and
18 your vote, and if you wish the explanation for your
19 vote. Remember the question. If you voted no, you
20 might wish to add what additional data should we
21 obtain.

22 DR. HATSUKAMI: Dorothy Hatsukami, and I voted

1 yes, primarily based upon a lot of postmarketing
2 surveillance information that was provided from Europe.
3 And it didn't seem like there were any major safety
4 issues. In terms of dependence, it seemed to be
5 comparable to other medications that are over the
6 counter.

7 DR. NEILL: Thank you. Dr. Parker?

8 DR. PARKER: I voted no because of my concerns
9 for abuse potential and misuse. I think use in younger
10 consumers would be very -- more data on use in young
11 consumers under the age of 18 in terms of its safety,
12 nicotine safety, in that age group would be needed
13 before I feel comfortable with making it available over
14 the counter.

15 DR. NEILL: Thank you. Dr. Roumie?

16 DR. ROUMIE: Christianne Roumie. I voted no
17 for the same reasons, essentially, the abuse potential
18 and the uncertain regulation among young users.

19 DR. NEILL: Thank you. Dr. Pruchnicki?

20 DR. PRUCHNICKI: Maria Pruchnicki. I voted no
21 for the same reasons that Dr. Parker and Dr. Roumie
22 stated.

1 DR. NEILL: Thank you. Dr. Di Francesco?

2 DR. DI FRANCESCO: Lorenzo Di Francesco,
3 Emory. I voted yes. I felt the data presented that
4 the use of the drug in the current population seemed
5 safe, although I have future, obviously, concerns that
6 are outside my vote regarding the adolescent
7 population.

8 DR. NEILL: I'm Richard Neill. I voted yes.
9 I think there's a very small present tolerable safety
10 signal. I don't share the concerns about abuse in the
11 under 18 age to the same extent. While I'm confident
12 some small amount may exist, my concerns are more about
13 transfer of addiction and transfer of use over time.

14 Dr. King?

15 DR. KING: Tonya King. I voted no, primarily
16 for the concerns about dependence, misuse, and abuse.
17 I think that if it were to be approved, it should be in
18 a much more controlled way. Also, just because someone
19 has a credit card and can purchase on Amazon doesn't
20 mean they're 18.

21 DR. NEILL: Thank you. Dr. Krinsky?

22 DR. KRINSKY: Dan Krinsky. I voted yes. I

1 felt comfortable with the safety data that was
2 presented from the findings in Europe and the
3 individuals that have used the product so far, and feel
4 comfortable with the safety data for the intended
5 audience here in the States. But I will say that I
6 have the same concerns about some of the abuse
7 potential.

8 DR. NEILL: Thank you. Dr. Farber?

9 DR. FARBER: Neil Farber, UC San Diego. I
10 struggled with this one more than the first question
11 because of the fact that I think a lot of the safety
12 data regarding adults is pretty clear. My major
13 concern is especially in the younger population and
14 especially with the increase in e-cigarettes. And I'd
15 like to see more data not only in terms of safety among
16 adolescents but also comparing a population of
17 adolescents using e-cigarettes and those not using
18 e-cigarettes, and how they viewed this particular
19 product.

20 DR. NEILL: Thank you. Ms. Mack-Brooks?

21 MS. MACK-BROOKS: Pamela Mack-Brooks. I voted
22 yes, based on the safety and available postmarket data.

1 Thank you.

2 DR. NEILL: Thank you. Ms. Thomas?

3 MS. THOMAS: Jill Thomas, patient
4 representative. I voted yes, however, I do believe
5 it's probably easy to abuse this product, but I think
6 the abuse of cigarettes is far more dangerous.

7 DR. NEILL: Thank you. Dr. Nelson?

8 DR. NELSON: David Nelson. I voted yes. I'm
9 not terribly worried about the transfer problem cause
10 I'd frankly rather have someone addicted to this drug
11 than cigarettes because I think cigarettes are far and
12 away more dangerous. I'm a little concerned about the
13 child issue, but we probably have more data on this
14 drug than we have on most drugs we approved, given how
15 long it's been available and in so many areas outside
16 the U.S.

17 DR. NEILL: Thank you. Dr. Shoben?

18 DR. SHOBNEN: Abby Shoben. I voted yes, again,
19 to reiterate the point that there's actually pretty
20 extensive safety data both in the clinical files and
21 from the extensive postmarketing, so I don't have a lot
22 of concerns.

1 DR. NEILL: Thank you. Dr. Curry?

2 DR. CURRY: Sue Curry. I also voted yes for
3 all the reasons that have already been given.

4 DR. NEILL: Thank you. Dr. Krishnan?

5 DR. KRISHNAN-SARIN: I voted no. I'm not
6 concerned about the safety of the product in the
7 intended populations. I am very concerned about the
8 potential for abuse of this product. I do not think
9 postmarketing surveillance data is sufficient to really
10 tell us it has not been used by youth because that
11 really depends on people reporting it, and probably a
12 lot of people don't report these things.

13 We need better surveillance systems. We have
14 a great surveillance system in the U.S., so if this
15 product goes into -- gets approved, I would suggest
16 that CDER should really partner with CTP and build
17 questions about this into the PATH study and other
18 longitudinal studies that are being done to really
19 monitor this use. And I think more importantly, we
20 need better qualitative data on the appeal of this
21 device to youth and have appropriate measures on the
22 labeling to deter use.

1 DR. NEILL: Thank you. So we have one last
2 question, question 7. This is, I think as Dr. Michele
3 mentioned, wrapping it all up together. Is the
4 benefit-risk profile of nicotine mouth spray,
5 1 milligram per spray, supportive of OTC use as a
6 smoking cessation aid. If yes, do you have additional
7 comments or recommendations for labeling? If no, what
8 further data should be obtained?

9 Do any of you have clarifying questions about
10 this? While you're thinking, Dr. Krishnan, I'm going
11 to thank you. I think this is the latest in the day a
12 comment about we should improve our postmarket safety
13 data has ever been made, but you got it in. Thank you.
14 So seeing no other comments, I'm going to open the
15 vote.

16 (Voting.)

17 LCDR CHEE: Question 7, we have 9 yeses,
18 6 noes, and zero abstain.

19 DR. NEILL: Thank you. So just to shake
20 things up, I'm going to start with me. We're going to
21 go this way, and then we're going to come around to my
22 left.

1 I'm Richard Neill. I voted yes, and I think
2 that the vote total reflects the comments that we've
3 heard earlier. I'd have nothing further to add to my
4 other comments.

5 Dr. King?

6 DR. KING: Tonya King. I voted no. I think
7 that it would be good to see a study that was more of
8 the Standard efficacy trial in the U.S., and I feel
9 that the quit rates that were seen in study 38 actually
10 indicate that is not effective. But I feel like if we
11 could replicate the results of study 11 in the U.S.,
12 that that could be promising. Thank you.

13 DR. NEILL: Thank you. Dr. Krinsky?

14 DR. KRINSKY: Dan Krinsky. I voted yes with
15 some trepidation. I still feel, big picture, that from
16 a public health perspective, the more options we can
17 offer to people who are interested in quitting, the
18 better chance we have of getting people off cigarettes.

19 DR. NEILL: Thank you. Dr. Farber?

20 DR. FARBER: Neil Farber, UC San Diego. I
21 voted no because of my feelings about, on the one hand,
22 concerns about labeling and whether patients could

1 really understand the instructions well enough to be
2 able to use this effectively, and the concerns about
3 the low percentage in study 38. On the other hand, my
4 concerns about the potential for abuse among
5 adolescents, and especially those who might be vaping.

6 DR. NEILL: Thank you. Ms. Mack-Brooks?

7 MS. MACK-BROOKS: Pamela Mack-Brooks. I voted
8 yes. I think based on the data that was presented and
9 my work with my organization on the community health
10 needs assessment, smoking cessation is a top 10 desire
11 in Philadelphia, PA, and that this will be another
12 option with guidance for people to stop.

13 DR. NEILL: Thank you. Ms. Thomas?

14 MS. THOMAS: Jill Thomas. I voted yes, but I
15 think that the steps should be clearer, and I think
16 that there should be a more clear-cut chart versus how
17 much you smoke, versus how many sprays a day that you
18 get as a guide going from one step to step 3.

19 DR. NEILL: Thank you. Dr. Nelson?

20 DR. NELSON: David Nelson. I voted yes. I
21 think that the positives outweigh the negatives. I
22 think it's relatively safe. I think the efficacy is

1 okay. It's not great, but I think it gives us another
2 tool to use in what is a public health disaster.

3 DR. NEILL: Thank you. Dr. Shoben?

4 DR. SHOBE: Abby Shoben. I voted yes.

5 Pretty much, my thoughts exactly echo Dr. Nelson's.

6 DR. NEILL: Thank you. Dr. Curry?

7 DR. CURRY: I voted yes. I think smokers will
8 vote with their feet on this product, and I think
9 there's really good potential but also some potential
10 issues that have already been discussed around labeling
11 and so forth. I just want to echo the importance of
12 postmarketing surveillance around youth uptake. I'm
13 not seeing something that I think is going to go there,
14 but I'm often sure and often wrong.

15 DR. NEILL: Thank you. Dr. Krishnan?

16 DR. KRISHNAN-SARIN: I voted yes because I
17 think the product does have the potential to help
18 smokers, and I'm basing my yes vote on that. That
19 said, I have specific recommendations for the label,
20 including modifying and improving the staged labeling
21 issue we discussed earlier. But I think the label
22 could also be modified, and I just had this thought to

1 actually make it less attractive and less appealing to
2 kids also.

3 For example, there's research that just came
4 out from my group. It shows that the presence of
5 pictures, like the mint leaves and the green color are
6 actually very appealing to kids and actually activate
7 the brain reward circuitry. So there could be things
8 that could be done to this product, the way it's
9 displayed and how it looks, to not make it look so
10 attractive, which could potentially reduce the appeal.

11 I think it also needs to have instructions
12 that CTP is using about nicotine being an addictive
13 compound. That's something they're requiring on all
14 tobacco products, and I think that should be required
15 on this also.

16 DR. NEILL: Thank you. Dr. Di Francesco?

17 DR. DI FRANCESCO: Lorenzo Di Francesco. I
18 voted no, and I don't disagree with a lot of the
19 positive comments about how to improve the product
20 going forward, but it was primarily based on the
21 efficacy data that I thought would be great to have a
22 robust replication that looked a little bit more in

1 line with prior trials.

2 DR. NEILL: Thank you. Dr. Pruchnicki?

3 DR. PRUCHNICKI: I voted no. Although I want
4 to believe in this product, I feel like I don't quite
5 have the confidence for the reasons that we stated
6 before, and I am significantly concerned about the risk
7 for misuse, especially in a very vulnerable population
8 of our young people. I hope those fears are
9 misfounded.

10 DR. NEILL: Thank you. Dr. Roumie?

11 DR. ROUMIE: uh, Christianne Roumie. I voted
12 no for a couple of reasons. The first is meeting the
13 efficacy standard based on the current labeling, which
14 I think can be overcome and improved with the prior
15 suggestions. But then really driving home the vote was
16 the safety standard.

17 Currently, I don't know that it's been met
18 with the adequate data, particularly in the abuse
19 potential. I think some of the issues that have been
20 raised, such as labeling it as this is an addictive
21 product would help. I don't know that that would deter
22 a 13 year old who was looking to try something new.

1 DR. NEILL: Thank you. Dr. Parker?

2 DR. PARKER: I voted no. I felt like the
3 risks outweigh the benefits. The efficacy was
4 marginal, if present, given the numbers and what we
5 reviewed, and the safety concerns in terms of abuse
6 potential, misuse, and the fact that it will be
7 available once it's over the counter. Advertising for
8 OTC products is not under the purview of this agency
9 but somewhere else, and I have big concerns about that.

10 Label comprehension studies I think did not
11 demonstrate adequate understanding of a complex
12 multi-step process that is needed for what was intended
13 to be safe and effective use. And though I love the
14 idea of postmarketing surveillance, I'm yet to see it
15 really have an impact on meaningful health outcomes.
16 I'm a hopeful person, too, but I'm not hopeful here.

17 DR. KRISHNAN-SARIN: It is happening with
18 e-cigarettes.

19 DR. NEILL: Thank you. Dr. Hatsukami?

20 DR. HATSUKAMI: Dorothy Hatsukami. I voted
21 yes because of the potential health benefit among
22 people that are the most disadvantaged nowadays. It is

1 the lower SES individuals that are smoking, that don't
2 have a lot of resources available to them. So I think
3 it's really important to give them choice in terms of
4 what may be effective products, which I do think that
5 there's demonstration that the nicotine mouth spray is
6 more effective than a placebo.

7 I think we also need to consider that
8 e-cigarettes is competition. Many of the smokers are
9 switching to e-cigarettes in order to stop smoking, and
10 at this point in time, they certainly aren't as
11 regulated nor have they gone through the rigorous types
12 of trials that GSK had implemented with the nicotine
13 mouth spray. So with all those variables, I voted yes.

14 DR. NEILL: Thank you very much.

15 I think we've now been through all of the
16 discussion and all of the votes. Before we adjourn,
17 are there any last comments from FDA?

18 DR. MICHELE: Just once again, an opportunity
19 to thank the committee, as well as to thank GSK and J&J
20 for their presentations today.

21 **Adjournment**

22 DR. NEILL: Thank you.

1 Panel members, please take all belongings with
2 you, as the room is cleaned at the end of the meeting
3 day. Anything you leave will be disposed of. Remember
4 to drop off your name badge at the registration table
5 on the way out so that we may recycle them. We will
6 now adjourn the meeting. Thank you.

7 (Whereupon, at 4:35 p.m., the meeting was
8 adjourned.)

9
10
11
12
13
14
15
16
17
18
19
20
21
22