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 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

May 2, 2013
 8:00 a.m.

Hilton Washington D.C. North
 620 Perry Parkway
 Gaithersburg, Maryland

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KARLA V. BALLMAN, Ph.D.	Voting Member
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KAREN E. BURKE, M.D.	Temporary Voting Member
ROBERT L. McCAULEY, M.D.	Temporary Voting Member
MICHAEL J. OLDING, M.D.	Temporary Voting Member
PIERRE M. CHEVRAY, M.D.	Temporary Voting Member
ELIZABETH PAIGE BROWN STRONG	Patient Representative
SHARON TIMBERLAKE, M.S.H.S., RAC, CCRA	Industry Representative
KRISTINE R. MATTIVI, M.S., PT	Consumer Representative
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MEETING

(8:06 a.m.)

DR. LoCICERO: I would like to call this meeting of the General and Plastic Surgery Devices Panel to order. It is now 8:06 a.m.

I'm Joseph LoCicero. I'm the Chairperson for this Panel. I am a general thoracic surgeon and Emeritus Professor at SUNY Downstate.

I would like to ask every member of the Panel to introduce themselves, including their area of expertise, their position, and their affiliation, starting with on my right.

DR. BALLMAN: Hi, I'm Karla Ballman. I am a statistician from Mayo Clinic, Rochester, Minnesota.

DR. ALAM: Hi, I'm Murad Alam, and I'm a dermatologist from Northwestern University in Chicago.

DR. BURKE: I'm Karen Burke. I'm a dermatologist in New York, at Mount Sinai Medical Center.

MS. MATTIVI: Hi. Kris Mattivi. I'm the Consumer Rep on the Panel, and I'm a manager of analytical services at the Colorado Foundation for Medical Care.

MS. STRONG: I'm Paige Brown. I am the Patient Representative.

MS. TIMBERLAKE: Good morning. I'm Sharon Timberlake. I'm the Industry Representative. I am the VP of Regulatory and Quality Affairs for

OmniGuide.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. MILLER: I'm Michael Miller. I'm a plastic surgeon and the Chair of the Plastic Surgery Department at the Ohio State University.

DR. McCAULEY: Rob McCauley. I'm Professor of Plastic Surgery at the University of Texas Medical Branch in Galveston, and Chief of Plastic Surgery Services at the Shriners Hospital.

DR. OLDING: Michael Olding. I'm Chief of Plastic Surgery at George Washington University.

DR. CHEVRAY: Pierre Chevray. I'm a plastic surgeon at the Methodist Hospital in Houston, Texas.

MR. MELKERSON: I'm Mark Melkerson. I'm the Acting Director of the Division of Surgical Devices with the FDA, and I'm a biomedical engineer.

DR. LoCICERO: I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application P110033, Allergan Juvéderm Voluma XC.

Before we begin, I would like to ask our distinguished Panel members and FDA staff -- I'm sorry, I think we have done that.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

And Ms. Jamie Waterhouse, the Designated Federal Officer for the General and Plastic Surgery Devices Panel, will make some introductory remarks.

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws.

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Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Allergan for the Juvéderm Voluma XC indicated for deep implantation to restore lost volume in the mid-face for aesthetic improvement. This meeting is classified as a particular matter involving specific parties.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S.C. 208.

A copy of this statement will be available for review at the

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registration table during this meeting and will be included as a part of the official transcript.

Sharon Timberlake is serving as the Industry Representative, acting on behalf of all related industry, and is employed by OmniGuide.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the General and Plastic Surgery Devices Panel for the duration of this meeting on May 2nd, 2013:

Dr. Alam, Dr. Burke, Dr. McCauley, Dr. Olding, and Dr. Chevray.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Dr. LoCicero to act as Temporary Chairperson for the duration of this meeting.

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This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on April 24th, 2013.

For the duration of the General and Plastic Surgery Devices Panel meeting on May 2nd, 2013, Ms. Elizabeth Paige Brown Strong has been appointed as a temporary non-voting patient representative. For the record, she serves as a consultant to the Oncologic Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the materials to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on April 29th, 2013.

Before I turn the meeting back over to Dr. LoCicero, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

The press contact for today's meeting is Morgan Liscinsky.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and

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have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. Claire Karlson at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

Dr. LoCicero.

DR. LoCICERO: We will now hear a brief presentation from the FDA's Division of Surgical Devices.

DR. DANG: Good morning. My name is Jiyoung Dang, and today I'll be presenting a brief summary of activities for the division since the last Panel meeting, which was held in April 2011 for the Restylane product.

Recently, the Center for Devices and Radiological Health went under a major reorganization that went into effective in November 2012, which affected most of the units within CDRH. Within the Office of Device Evaluation, the reorganization resulted in the creation of seven divisions with many new branches that were established as part of this reorganization effort.

The former Division of Surgical, Orthopedic, and Restorative Devices was split into three new divisions, the Division of Orthopedic Surgery, the Division of Neuro and Physical Medicine Products, and the Division of Surgical Devices.

The Division of Surgical Devices consists of the former Plastic and Reconstructive Surgery Branch and the General Surgery Devices Branch, and each of these branches were divided further into two branches, with rough device type splits shown on this slide. The division consists of 29 scientific review staff across the board, as well as seven medical officers, and currently many of the management positions are filled on an acting basis.

Some notable approvals and clearances in the past couple years have been two breast implant PMAs, the Sientra Silicone Gel Breast Implants and the Allergan Natrelle 410 Highly Cohesive Breast Implants.

We also had a new type of filler approved, the Merz Belotero Balance, which is an HA filler, as well as a new indication for lip augmentation for the Medicis Restylane injectable and the Restylane-L injectable.

We have also had several PMAs complete a post-approval study and update their labeling to reflect the data that were collected through their PAS.

We have also had a recent 510(k) clearance for the Arcos Burn Resuscitation Decision Support System, which is intended for use in predication of hourly fluid volume.

On the general surgery side we have, back in 2011, approval for the MELA Sciences MelaFind device. And the Dune Medical MarginProbe System and the InSightec ExAblate System were approved in 2012.

So with that, I'll conclude my presentation, and I look forward

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to a lively discussion.

Thank you.

DR. LoCICERO: Thank you.

We will now proceed to the Sponsor presentation from Allergan.

DR. AVELAR: Mr. Chairman, members of the Committee, and members of the Food and Drug Administration, good morning. My name is Rui Avelar. I'm the Chief Medical Officer for Allergan Medical.

I'm ahead of myself. Okay, I apologize. Mr. Chairman, I'll try that again.

Members of the Committee, good morning. My name is Rui Avelar. I'm the Chief Medical Officer for Allergan Medical.

We're here today to review the data that support the use approval for Juvéderm Voluma XC. It's an injectable gel to correct age-related volume deficit in the mid-face. For today's presentation, we'll refer to Juvéderm Voluma XC as Voluma. Voluma has been approved around the world since 2005 and has a long history of safe and effective use.

Here, on the left, is a "before" photograph to illustrate what mid-face volume deficit is, and on the right an "after" photo to demonstrate the type of correction that can be achieved with Voluma.

Historically, dermal fillers for cosmetic use have been used largely focused on filling wrinkles and folds. Dermal fillers are injected into

the skin through a fine needle. They work by taking up space under the skin. When injected into a wrinkle, as shown here, they push up against the skin, resulting in a smoother surface. The same principle is employed for correcting age-related mid-face volume deficit.

Dermal fillers have been used for decades in the United States. The first FDA-approved dermal fillers were made of collagen, with bovine collagen in the early '80s, followed by human collagen in 2003, and finally porcine collagen in 2008.

Hyaluronic acid fillers, commonly referred to as HA fillers, were the next generation. The FDA has approved nearly a dozen HA-based fillers. The first FDA-approved HA filler was Restylane in 2003. And Allergan's Juvéderm was approved in 2006. Most recently, FDA approved an expanded indication for Restylane that now includes lip augmentation.

Three synthetic fillers have also been approved by the FDA. Sculptra, which is polylactic acid, was approved in 2004 for HIV lipoatrophy and then for wrinkles and folds in 2009. Artefill, made of polymethylmethacrylate microspheres, was also approved for the correction of wrinkles and folds in 2006. And Radiesse, a calcium hydroxylapatite-based filler, was approved in 2006 for HIV lipoatrophy and for wrinkles and folds.

Today, HA products are the most commonly used fillers in the United States. Of the nearly two million soft tissue filler procedures performed in the United States in 2012, more than 70% were done with HA

products. HA fillers have a strong majority of market share due to their long duration, history of safe use, and a natural look and feel they provide.

In addition to the long and proven track record of treating wrinkles and folds, there's also substantial clinical experience outside the United States using HA to treat mid-face volume deficit. For example, in Europe, market research shows that HA fillers are used in about five out of six procedures for increasing mid-face volume. HA fillers have a proven performance that has led them to become the most commonly used fillers globally.

Currently there are no products approved in the U.S. that are indicated for correcting age-related mid-face volume deficit. The result is that the available products are being used off label. In fact, market research conducted in 2012 found that one in five dermal filler patients received treatment in the cheeks. However, none of the current fillers that are available in the United States are ideal for mid-face volume correction. HA fillers like Juvéderm are among those used off label. But these current formulations for wrinkles and folds are also not optimized for mid-face volume correction.

Let me give you some background on HA fillers to better explain this.

Hyaluronic acid is a naturally occurring polysaccharide, or sugar, that is present in the skin. The most important characteristic of

hyaluronic acid relevant to its performance as a dermal filler is its ability to bind to large quantities of water, and HA fillers essentially work by this ability to bind to water and displace the tissue. In its native form, HA has a fast turnover with a half-life of two to three days. In its natural state, hyaluronic acid is linear or, in other words, it's not cross-linked. And in order to make HA persist, it needs to be cross-linked. All FDA-approved hyaluronic acid fillers employ a cross-linking molecule, most commonly BDDE. Voluma uses the same cross-linking molecule.

Voluma is formulated from the same raw materials as other Juvéderm products which are already FDA approved for the treatment of facial wrinkles and folds. In addition to using the same cross-linker, both Juvéderm and Voluma have been formulated with .3% lidocaine to enhance patient comfort.

The primary difference in the raw materials is that Voluma is produced using a mixture of both high and low molecular HA, whereas Juvéderm uses only high molecular weight HA. Voluma uses less cross-linker material and has a lower overall HA concentration.

Voluma was developed to leverage many of the characteristics of the currently approved Juvéderm formulations with modified physical properties that are tailored for the use to correct age-related mid-face volume deficit. A volumizing application involves injecting higher volumes in a deeper plane than what's used for correcting wrinkles and folds.

To tune Voluma for treating mid-face volume deficit, we specifically looked at adjusting two parameters, cohesivity and gel hardness or G prime.

In Voluma, cohesivity and gel hardness are balanced to make a firmer, more robust product that's still easily extruded through a fine-gauge needle. If we compare Juvéderm and Voluma, we see that Voluma has a lower cohesivity and a higher G prime. Both products are provided in a 1 mL syringe with a 27-gauge half-inch needle. Voluma can also be injected with a 25-gauge one-inch needle.

To give some context around gel hardness, this graph shows the G prime of liquid hand soap, jam, and peanut butter. Liquid hand soap is about 40 Pa, jam is about 250 Pa, and peanut butter is about 3,000 Pa. As you can see from the figure on the right, Voluma has a gel hardness of approximately 300 Pa, which is about 50% higher than Juvéderm, but is still a soft gel with a hardness comparable to jam.

As with the approved Juvéderm formulations, Allergan conducted the full range of biocompatibility studies and assessments for Voluma. The tests outlined here were done in accordance with ISO 10993. Voluma has an acceptable biocompatibility profile, as is required for long-term implantable devices. During these tests, where appropriate, an approved Juvéderm formulation was used as a reference control due to its long history of safe clinical use. In all of these tests, Voluma was found to be

in compliance with the international standards and Allergan's internal standards for product qualification.

As we review the data today, we see that Voluma is safe and effective in correcting age-related mid-face volume deficit. In fact, Voluma has a long history of safe use globally. It received CE mark in Europe in 2005 for the formulation without lidocaine, and then in 2009, Voluma with lidocaine was CE marked. It's currently approved and marketed in Europe, Canada, Australia, and numerous other countries. Since 2005 more than 520,000 syringes have been distributed, representing significant clinical experience.

With this background in mind, I'd like to review the agenda for the rest of today's presentation.

Dr. Todd Gross from Allergan will introduce the key components of the design of our pivotal study.

Dr. Derek Jones, one of the study investigators, will present the effectiveness results from the study. Dr. Derek Jones is a Clinical Associate Professor of Dermatology at UCLA and founder and director of Skin Care and Laser Physicians. He's participated in many of the pivotal clinical trials on injectable fillers and has widely published on the topic and is the editor of a recent special issue on fillers in a peer review journal, *Dermatologic Surgery*.

I'll then return and present the data on common treatment site responses and adverse events and provide an overview of our post-approval

study proposal.

Throughout our presentation we'll present data to address the five main FDA Panel discussion questions. Prior to presenting specific data and analyses to address the FDA discussion questions, we'll present a slide with a blue background to summarize the question.

In addition to our presenters, we've invited other subject matter experts to assist us in answering your questions.

Dr. Julius Few is a board certified plastic surgeon and was also a study investigator. Dr. Massimo Signorini has extensive experience in using Voluta outside the U.S., where Voluta has been approved for a number of years. Dr. Dan McLain is a clinical toxicologist. Dr. Glenn Fredrickson is a materials specialist. And Dr. Amy Tezel was the director of regulatory affairs at Allergan responsible for the Voluta project. She's currently an independent regulatory consultant.

All of our outside experts have been compensated for assisting us in preparation for this meeting.

At this time I'd like to invite Dr. Todd Gross to the lectern to review the Voluta trial design.

DR. GROSS: Thank you, Dr. Avelar.

Good morning, everyone. I'm Todd Gross, Senior Director of Biostatistics for Allergan, and Associate Professor of Statistics at the University of California, Santa Barbara. I'll be presenting the study design of

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the Voluma pivotal clinical trial.

The Voluma pivotal study was a multicenter, single-blind, randomized controlled trial examining the safety and effectiveness of Voluma for cheek augmentation to correct age-related mid-face volume deficit.

Subjects were recruited from geographically diverse locations which, in general, track the population patterns in North America. Fifteen study sites enrolled a total of 345 subjects. Average enrollment was 20 subjects per site, with the lowest enrolling 14 subjects and the highest enrolling 37.

Because there are no dermal fillers currently approved for this indication in the United States, the FDA suggested using a control group of subjects who did not receive treatment but who were assessed for effectiveness. We'll refer to this as the no-treatment control design. A similar no-treatment control design was used in the pivotal study of Restylane for lip augmentation.

In the Voluma trial, subjects in the control group did not receive treatment until after assessment of the primary endpoint at six months. This delayed treatment was incorporated to provide an incentive for subjects randomized to the control group to remain in the study.

In order to implement a blinded trial using a no-treatment control group, it was necessary to separate the treatment of subjects from the evaluation of effectiveness. As a result, each site had three study

investigators, one who treated subjects and two blinded evaluators, for a total of 45 study investigators.

The treating investigator was responsible for all study activities except for the evaluation of effectiveness. They recruited and consented subjects and determined their eligibility for the study. Once a subject was enrolled, the treating investigator discussed treatment goals with the subject and then injected Voluma to meet these goals. Finally, the treating investigator monitored subject safety throughout the course of the study.

In order to maintain the blinding of the treatment assignment of subjects, the evaluation of effectiveness was not performed by the treating investigator. Instead, two blinded independent evaluating investigators at each site assessed the effectiveness of Voluma. They were primarily board certified dermatologists or plastic surgeons. They each met separately with the subject to assess the pre-specified primary and secondary effectiveness endpoints throughout the course of the study.

The Mid-Face Volume Deficit Scale, or MFVDS, was used by the evaluating investigators to determine the primary effectiveness measure and also by the treating investigators to determine eligibility for the study.

The MFVDS is a validated six-point rating scale consisting of two parts, photometric images and verbal descriptions for each grade. You have an exact duplicate of the photometric scale used by investigators to determine MFVDS ratings during the clinical study with the slides that we

handed out today.

Now, here you can see some of the prototypical pictures used to define the Mid-Face Volume Deficit Scale. From these photos you can see the progression of the scale from left to right on this slide, starting with a deficit of "none," described as moon face or with fullness or convexity, on the left, to a severe deficit, described as "wasting" with severe concavity, on the right.

Each of the evaluating investigators used this photometric scale to rate subjects' mid-face volume deficit at baseline and at each study follow-up visit. In order to reduce variability and improve the accuracy of the scale ratings, the two evaluator ratings were averaged at each time point.

In order to be eligible for the study, a subject needed to be between 35 and 65 years of age, and the treating investigator had to determine that the subject had an overall mid-face deficit of at least three, indicating moderate deficit or greater.

At the FDA's request, we defined facial subregions that could be used to capture treatment safety and effectiveness data. Three mid-face regions were defined, the zygomaticomalar region, the anteromedial cheek, and the submalar region. Since all outcomes were similar across these facial subregions, we'll focus today on results for overall mid-face volume deficit.

At the Month 6 visit, subjects were seen independently by each of the two evaluating investigators at their site. Using the MFVDS

photometric guide, each evaluator determined the subject's Mid-Face Volume Deficit Scale score. When subjects came in for their visit, the evaluating investigator independently examined the subject in person and then compared them to this photometric scale to determine their MFVDS score.

To be clear, the evaluating investigators did not have a baseline photo of the subject, nor did they have the baseline rating when they evaluated subjects for the primary endpoint.

As suggested by the FDA, improvement in mid-face deficit was determined by taking the average of the two blinded evaluating investigator assessments at Month 6 and subtracting their baseline average.

The primary effectiveness endpoint of the study was the percent of subjects who demonstrated at least a one-point improvement from baseline to Month 6 in their overall Mid-Face Volume Deficit Scale score.

As agreed with the Agency, Voluta was considered to be clinically effective if at least 70% of the subjects in the treatment group were responders and the treatment group responder rate was statistically superior to the responder rate for the no-treatment control group.

In addition to the primary endpoint, the study included multiple effectiveness endpoints assessed by evaluating investigators, treating investigators, and the subjects themselves. Some of these endpoints

will be presented here today, and others are detailed in the briefing book. As you will see, all effectiveness endpoints support the conclusion that Voluma is effective for mid-face volume correction.

Turning now to the exclusion criteria for the study, subjects were ineligible if they had had prior permanent or semi-permanent facial aesthetic procedures or prior temporary facial aesthetic procedures within a predefined washout period. For example, subjects could not have been treated with temporary injectable fillers in the mid-face within 12 months of study enrollment. Finally, subjects were not eligible for participation if they had very thin skin in the mid-face region or if their mid-face volume deficit was caused by something other than aging, such as congenital defects or HIV.

Next, I'd like to present a graphic overview of the study design. I'll first focus on study visits up to the Month 6 primary endpoint assessment.

After subjects had their baseline MFVDS assessed independently by the two evaluating investigators, they were randomized either to the treatment group or the control group. Treatment group subjects received their initial treatment from the treating investigator and one month later saw the treating investigator for an optional touch-up treatment to ensure that optimal correction had been achieved. Six months after initial treatment or optional touch-up treatment, if performed, the subject's overall MFVDS score was evaluated by the blinded evaluating investigators for the primary endpoint of the study.

Most of the data presented here today are based on evaluation at six months from the last treatment, as this was the time point agreed upon with the FDA for the primary endpoint analysis.

Note that three days after treatment, subjects were contacted by phone to assess safety. In-person clinic follow-up visits then occurred at months one and three and quarterly for up to 24 months. At each of these visits the treating investigator assessed the subject for any safety events, and then separately each evaluating investigator saw the subject for assessment of effectiveness.

Now, subjects randomized to the control group did not receive treatment for the first six months of the study. At their study visits, control subjects were evaluated for effectiveness by each of the blinded evaluating investigators, just as the treatment subject had been. At Month 6, each control subject's overall MFVDS score was evaluated for the primary endpoint. Once their Month 6 assessments were complete, control subjects then received treatment and followed the same post-treatment visit schedule as the treatment group subjects, including an optional touch-up treatment one month after initial treatment.

All treated subjects were allowed to undergo a repeat treatment between 12 and 24 months after initial treatment, if their MFVDS had returned to pre-treatment levels. At Month 24, all subjects who had not already received repeat treatment were offered it regardless of their

correction status. All subjects who received repeat treatment are being followed for an additional 12 months.

The Voluma trial enrolled a total of 345 subjects. Of those enrolled, 329 were found to be eligible for the trial. The first two subjects at each of the 15 sites were not randomized but rather received treatment as run-ins to ensure that their physicians and staff were adequately trained. This left 299 subjects available for the 5:1 randomization.

After randomization, but prior to treatment, 17 subjects withdrew from the treatment group. Forty-seven subjects were randomized to the control group. Six subjects in the treatment group and seven subjects in the control group discontinued before the Month 6 visit. There were also 21 subjects in the treatment group and four subjects in the control that had missing values at Month 6, or whose visit was outside the window for the primary endpoint assessment.

At the close of the Month 6 window, there were 208 evaluable subjects in the treatment group and 36 evaluable subjects in the control group. For the balance of our presentation, all effectiveness analyses, unless otherwise noted, will be based on these observed cases.

The randomized subjects were primarily female, with a median age at study entry of 56 years in the treatment group and 55 years in the control group. Slightly more than half were of Caucasian descent, and the racial distribution was similar across the two study groups. At baseline most

subjects, 94% in the treatment group and 96% in the control, had either moderate or significant mid-face volume deficit, and the distribution of baseline deficit was evenly balanced between the treatment and control groups.

Approximately half of the treatments were performed with a 27-gauge needle and the other half with a 25-gauge needle. Injections were allowed in the subcutaneous and supraperiosteal planes, and 86% of the subjects were injected in both of these planes. The injection techniques were consistent with those used with currently available fillers, such as tunneling, fanning, and serial puncture. Eighty-two percent of subjects received the optional touch-up treatment 30 days after initial treatment to ensure optimal correction.

At initial treatment, the mean volume injected was 5.2 mL; 221 subjects received the optional touch-up treatment and on average received an additional 2 mL of Voluma. Overall, the total volume injected between initial and touch-up treatments was 6.8 mL, with a range of 1.2 mL to 13.9 mL.

With this background in mind, I'd like to turn the presentation over to Dr. Jones, who will present the clinical effectiveness results from the study.

DR. JONES: Thank you, Dr. Gross.

Good morning. I'm Derek Jones. I have a great deal of

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experience and interest in injectable filler research and have performed thousands of procedures to correct wrinkles and folds using all of the products mentioned by Dr. Avelar.

As many of us know from our clinical experience, fillers are commonly used in the United States for mid-face volume deficit, although they have not been studied or shown to be safe and effective for this indication in controlled clinical trials. I will present data that demonstrate that Voluma fills an unmet need for a formulation optimally designed for this indication.

As Dr. Gross outlined a few minutes ago, Voluma was considered to be clinically effective if at least 70% of the subjects in the treatment group were responders. In addition, the treatment group responder rate had to be statistically superior to the responder rate for the no-treatment control group.

The primary endpoint was met; 85.6% of the treatment group improved by one grade or more, with the lower confidence limit above the pre-specified 70% threshold. And there was a statistically significant difference between the treatment and control group responder rates.

As Dr. Avelar mentioned, we'll be specifically reviewing the FDA's discussion questions. The first question we will address is the validity of the Mid-Face Volume Deficit Scale. FDA points out that the evaluators often did not agree on the rating of a given subject, that the subject's

Month 6 MFVDS ratings indicated improvement less frequently than the ratings of the independent evaluators and that the no-treatment control group had a 39% response rate.

Let's first review the evaluator's agreement.

Similar to other clinical rating scales, the MFVDS does possess some subjectivity. Variability in this scale was expected, which is one of the reasons the Sponsor and the FDA agreed to use the average of the two investigators' readings at each time point.

I'd like to present an example of how two investigators can come up with two slightly different scores but still agree on the amount of correction.

Here are baseline photos of a subject from the Voluma trial along with the MFVDS rating guide below. Each evaluating investigator met with this woman live and compared her facial characteristics to the Mid-Face Volume Deficit Scale. As shown on the bottom of the slide, at baseline, one evaluating investigator rated her as a 3, or moderate, and one rated her as a 4, or significant, at baseline. And most of us would likely agree that she is a little worse than a 3 and a little better than a 4. The evaluating investigators needed to pick a number from the scale. One was a little more generous and one a bit more conservative. For the trial, the average of the two evaluating investigator scores was used, for a baseline score of 3.5.

At six months the evaluating investigators saw the woman

again. One rated her as a 1, or minimal, and one rated her as a 2, or mild, and we can probably agree that she is between a 1 and a 2 on the photometric scale. So although evaluating investigators disagreed on the absolute Mid-Face Volume Deficit Scores, they were in agreement in the change in mid-face volume deficit and, more importantly, they agreed that this subject is a responder.

Being able to define a subject as a responder is the most important use of the Mid-Face Volume Deficit Scale. That is the basis of the primary endpoint.

Let's look at another example. This time two evaluating investigators agreed on the baseline score but not the Month 6 score. Here are the baseline photos. Both evaluating investigators agreed that the subject was a 3, or moderate, at baseline. At Month 6, one evaluating investigator scored the subject as a 1, or minimal, and the second scored her as a 2, or mild. Here the evaluating investigators did not agree on the absolute rating, but they did agree that the subject was a responder. The primary endpoint analysis was based on the change in the average score.

Remembering that responder status is the basis of the primary endpoint, a more stringent analysis could require that both evaluating investigators agree that the subject was a responder. So we repeated the primary analysis using this more stringent responder definition and found that the treatment group responder rate was 75.6% and the control group

response rate dropped by two-thirds to 14.3%. This result confirms that even when we required both evaluating investigators to agree, there is still a clear demonstration of the effectiveness of Voluma.

Next, I'd like to address the disagreement between how subjects rated themselves on the Mid-Face Volume Deficit Scale versus the evaluating investigators.

The Mid-Face Volume Deficit Scale is a clinical tool designed for physicians and depends on clinical assessment, such as degree of concavity of the mid-face, recognition of bony landmarks, and an assessment of the underlying muscular structures. Subjects were not familiar with these anatomical landmarks; therefore, some disagreement is to be expected.

Perhaps a more appropriate measure for subjects is the Global Aesthetic Improvement Scale, or GAIS. The GAIS is a five-point scale that asks subjects a simpler and more relevant question. How much has your mid-face or cheek volume improved?

Responders were subjects who had a score of 1 or 2 on the scale, indicating their appearance was either "improved" or "much improved" at the six-month visit. Both subjects and evaluating investigators used the scale to compare Month 6 results with the baseline subject photo.

The responder rate based on the Global Aesthetic Improvement Scale demonstrates that Voluma was effective in restoring volume and improving appearance, with evaluating investigators rating 82% of the

subjects as "improved" or "much improved" from baseline. This was a secondary endpoint of the study.

Importantly, using the same grading scale, 93% of the treatment group subjects rated themselves as either "improved" or "much improved." Control subjects did not perform the GAIS self-assessment.

Finally, I would like to address the issue of the no-treatment control group response.

The Voluma protocol anticipated the possibility of as much as a 40% control group response, which supported the requirement to show statistical significance between treatment and control groups.

Control group response is common in clinical trials of this type. In fact, similar results were seen recently in the Restylane lips clinical trial, presented to this Panel in 2011, where there was a 37% response rate in the no-treatment control at 24 weeks.

Finally, three subjects were randomized to the control group but actually received treatment in error, and two of them provided data for the primary endpoint. Because the primary effectiveness analysis was performed as randomized, data from these treated control subjects remained in the control group and inflated the control group response rate.

One way to reduce a control group response rate is to raise the threshold used to define the clinical response and thereby reduce the effect of the scale variability. Therefore, to better understand the control group

response, here is an analysis of response by increasing thresholds of improvement in Mid-Face Volume Deficit Scores from baseline.

The first set of bars represent the primary endpoint, the proportion of subjects achieving at least a one-point change in Mid-Face Volume Deficit Score. Then, for comparison purposes, we plotted responders at half-point increments in the response definition. You can see that as you reduce the impact of subjectivity of the scale by increasing the Mid-Face Volume Deficit Score threshold, the effect size remains constant. In other words, regardless of the threshold that defines a clinical response, the treatment group response is always significantly different than the control group. The difference between the treatment group and control group is dramatically maintained, though the control group response is dramatically reduced.

In addition to the high responder rate at Month 6, another characteristic of Voluta is its long duration of effect, and the Agency has posed a question related to this. The FDA has asked the Committee to discuss the limitations of effectiveness evaluations in the absence of a blinded control to detect clinically meaningful product performance after Month 6. FDA is also asking the Panel to discuss an appropriate study design to evaluate long-term effectiveness of products like Voluta for this indication.

And we agree with the FDA that the lack of a control group

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after six months was a limitation of the study. However, attempting to maintain a control group beyond six months would likely have led to a higher control group dropout rate because subjects want to receive treatment. A high dropout rate would have made the data challenging to interpret.

In the Voluma trial, subjects in the control group did not receive treatment until after assessment of the primary endpoint at six months. This delayed treatment was incorporated to provide incentive for subjects randomized to the control group to remain in the study.

As Dr. Gross mentioned earlier, because there are no dermal fillers currently approved for this indication in the United States, the FDA suggested using a control group of subjects who did not receive treatment but who were assessed for effectiveness. A similar no-treatment control design was used in the pivotal study of Restylane for lip augmentation.

174 treatment group subjects completed the Month 24 visit. Using this long-term data, we performed an analysis of the observed responder rate data from the Voluma pivotal trial. This analysis does not directly address the lack of a control group, but it does provide support for the duration of Voluma effectiveness. These data points depict the probability of maintaining collection for the treatment group at each time point.

The duration of effectiveness was determined using a Kaplan-Meier analysis to estimate the probability of retaining at least a one-point

improvement on the Mid-Face Volume Deficit Scale. The plot shows that just over half of treated subjects maintain this effect at month 21. The model further predicts that the probability of maintaining correction will go to zero by month 30.

The control group response at Month 6 was 38.9%, and a reasonable assumption would be that the control group response would not be different at later time points.

In addition to examining the duration of effect with this analysis, we were also interested to see the subject's perception of improvement over time. The red line represents the duration of effectiveness using a Kaplan-Meier analysis to estimate the probability of retaining a score of "improved" or "much improved" on the Global Aesthetic Improvement Scale. As you can see, both analyses suggest that Voluma continues to provide improvement over the course of the study.

To understand the duration of Voluma outside of the pivotal clinical study, we conducted a retrospective look at cases from the two clinical study sites in Canada, where Voluma was approved in late 2008 and is available commercially. These two sites have performed repeat Voluma treatment on approximately 1400 patients. While these data have not been previously supplied to the Agency for review, the sites reported that, on average, these patients returned for repeat treatment at 18 months. This supports the effectiveness results seen in the study beyond the Month 6 time

point, where the control group received treatment.

In summary, both measures of the primary effectiveness endpoint were met. Approximately 86% of subjects in the treatment group were responders on the Mid-Face Volume Deficit Scale, and the difference was statistically significant compared to the control group.

We also examined the level of agreement on responder status between evaluating investigators and found that the two evaluating investigators agreed that 75.6% of treatment group subjects were responders. This more stringent definition still results in clinically meaningful and statistically significant results.

The control group response was anticipated and does quickly diminish when we look at more stringent measures of effectiveness. The effectiveness of Voluma is also supported by the high and consistent Global Aesthetic Improvement Scale scores by both the investigators and, importantly, the subjects treated in the study.

Finally, the high response rate in the treatment group continues well beyond Month 6 and is estimated to last about 21 months.

Dr. Avelar will now return to present safety data from this pivotal study.

DR. AVELAR: Thank you, Dr. Jones.

Our data for common treatment site responses and adverse events are based on all reports from all subjects from the initial treatment

until the study exit or optional repeat treatment. This population includes all 270 subjects randomized and treated, including 235 in the initial treatment group, three from the control group who were treated in error at the start of the study, and then 32 subjects from the control group who crossed over to treatment after the Month 6 evaluation; 265 subjects completed the daily diary, which was the method of collecting the common treatment site responses.

Shown here is an image of the daily diary that was used by the subjects to record common treatment site responses such as injection site pain, tenderness, lumps and bumps. These common treatment site responses are expected considering subjects, on average, are being treated with almost seven 1 mL injections.

If I zoom in, you can see that the diary was meant to encourage collection of data. Subjects were prompted to report events and the severity of the symptoms related to the procedure in these daily diaries, so one would expect a fairly thorough representation of symptoms. In addition, each of the six treatment subregions were recorded and counted separately.

It's important to understand that, after a dermal filler procedure, the soft tissue undergoes a predictable healing process that involves multiple stages such as bleeding, inflammation, and proliferation. These events can manifest clinically as bruising, swelling, pain, and tenderness. Depending on the extent of the procedure, these healing stages

can take from a few days to a few weeks, and four to six weeks is often a normal time frame for healing. And this is what we saw in the Voluma trial.

We have proposed that multiple tables and verbiage be included in the label to explain common treatment site responses, including the incidence rate, severity, and duration of the responses. The label will also report these common responses as they relate to the initial treatment, the touch-up treatment, and the repeat treatment.

In their question to the Panel, the FDA highlights that 20% of common treatment site responses lasted beyond 30 days, and 78.4% were moderate to severe in nature. The FDA also points out that the device-related AEs occurred in 32.6% of subjects and most resolved within 60 days.

I'll first address common treatment site responses, starting with the percentage of subjects with common treatment site responses lasting beyond 30 days.

As seen here, this percentage is being driven primarily by subjects reporting a feeling of lumps and bumps at a rate of 16% and firmness at a rate of 12%. These daily diary entries often reflect the feeling of the underlying material after the procedure. The reports were generally mild or moderate in nature, and the vast majority resolved without treatment. Of these subjects who reported lumps and bumps or firmness lasting more than 30 days, 98% rated themselves as "improved" or "much improved" on GAIS at six months. The FDA commented that 78.4% of the common treatment site

responses were moderate to severe.

As is typical in dermal filler studies, most subjects experienced common treatment site responses. This table shows the incidence of all subject-reported common treatment site responses with the severity of moderate and severe. There are two main contributors to these responses: those that are reflective of the subject simply feeling the underlying material, reports such as lumps and bumps and firmness, and those consistent with the procedure that involves injection into the soft tissue, such as tenderness to touch, pain, and swelling.

To specifically address the FDA concerns, I'd like to first review the severity and duration of all common treatment site responses combined. Then I'll review the severity and duration of firmness, lumps and bumps, the two common treatment responses often associated with actually feeling the underlying material. And then I'll review the severity and duration of the remaining common treatment site responses, those associated with the healing.

Here we're showing the percent of subjects who experienced any common treatment site response broken down by severity. The severity shown here is the peak severity at any time point. It does not mean that the peak severity was maintained for the entire duration of the event.

78.4% of subjects reported one or more moderate or severe common treatment site responses. However, the median time to complete

resolution of the moderate and severe events was six days. Importantly, the median number of days where the subject rated the event as moderate or severe was only one day. In other words, the event either resolved or improved to mild in one day.

Turning now to CTRs that are associated with feeling the underlying material, let's look at the severity and duration of firmness, followed by lumps and bumps.

Here we've displayed the data for firmness on the left and lumps and bumps on the right. Focusing on moderate and severe reports, we see that the median duration is seven days for firmness and eight days for lumps and bumps, and the median time at moderate to severe was two days.

Now let's look at CTRs reflective of the healing phenomenon. These include bruising, tenderness, swelling, pain, redness, and discoloration. We can see that the severity of common treatment site responses for most of these events were mild to moderate.

As a reminder, each bar represents data on subjects who have reported the particular common treatment site response.

For all of these moderate and severe common treatment site responses, the median time to complete resolution was one week or less. Importantly, the median number of days where the subjects rated the event as moderate or severe was only one to two days. In other words, this means that the event either resolved or improved to mild within one to two days.

Another way to understand common treatment site responses is to see if any action was taken to treat the events, and if so, what it was. In nearly 98% of the cases, no action was taken. This is likely due to the mild to moderate severity of the reports.

In summary, the nature, severity, and duration of common treatment site responses reported by subjects in the Voluta trial were as expected with this type of treatment and indicated that Voluta treatment is well tolerated by the vast majority of subjects.

Next, I'd like to review the adverse events reported in the study.

In the study there were two sources of adverse events. The first was the traditional method seen by most clinical trials where adverse events are noted by the treating investigator. And the second method was based on those daily diaries of predefined common treatment site responses completed by each subject.

Based on the design of our clinical trial, any subject reporting a common treatment site response ongoing after completion of the 30-day diary was automatically recorded as an adverse event, regardless of the severity or the duration of the response. In fact, 95% of all device-related adverse events were reported via the daily diaries.

First, I'll describe the nature of the adverse events that were deemed to be unrelated to treatment by the treating investigators. Then I'll

discuss adverse events related to treatment, providing an overview of the most common adverse events in treatment. Finally, I'll review case report summaries for the two mild AEs that had a late onset and all moderate and severe AEs that required treatment.

In the Voluma trial, it turned out that all serious adverse events are captured within "severe adverse events." There were no unanticipated adverse device effects.

Turning now to adverse events unrelated to the device or procedure, 89 of 270 treated subjects, or 33%, reported 228 unrelated adverse events. The most frequent events were nasopharyngitis and headache. Ten subjects reported serious adverse events that were deemed to be unrelated to Voluma.

Displayed here is a brief listing of the events reported. Most of the descriptions provide assurance that these events were not related to Voluma.

The second to last subject on the list is a 60-year-old female who developed inferior field vision loss. This event took place approximately seven months after the last injection. Specialists diagnosed the event as an optic nerve stroke. The last subject, a 65-year-old Hispanic male, died of a stroke one year after treatment. These two events were deemed to be unrelated to the study device.

Next, I'd like to review the events that were reported as device

or procedure related.

In their question to the Panel, the FDA points out that device- and injection-related adverse events occurred in 32.6% of subjects, with most resolving within 60 days. And we agree that, after initial treatment, 88 of the 270 treated subjects, or 32.6%, reported adverse events related to the device or procedure; 99% of these events were reported at the injection site.

Adverse events reported in different mid-face regions for a given subject were counted separately.

We can also look at unique adverse events where an event reported in multiple regions is counted only once; 174 unique device-related adverse events were reported, with 97% at the injection site. Importantly, 76% of device-related adverse events resolved within 60 days of onset.

The most commonly reported device-related adverse events were mass, induration, swelling, and pain at the injection site. All of these reports are really expected considering we're injecting a filler into the soft tissue of the cheek.

To further illustrate, we'd like to use photos. The top series of photos were taken pre-treatment, and the bottom series shows month one visit. This subject reported lumps and bumps of moderate severity lasting 52 days. The lumps and bumps represented two adverse events, as they were reported in the left and right submalar region. As evident in the photos, these events weren't visible, but they were palpable to the subject and the

investigator.

In order to better understand these device-related adverse events, we examined the case report forms and noted the actions taken to treat each event. Ninety-four percent of the time, the device-related adverse event did not require that any action be taken. Again, this is likely due to the mild to moderate severity of the majority of the adverse events. In most other cases, subjects received medication to treat the adverse event. In a few cases, subjects received ice or facial massage.

When we look at the resolution of the device-related adverse events, we see that 99% of the time the event resolved. This is consistent with the fact that the majority of adverse events were self-limited and did not require treatment.

One subject who reported ongoing firmness also reported that she was satisfied with her treatment outcome. This same subject also chose to receive repeat treatment.

Next, I'll review case report summaries for the two mild AEs that had a late onset and all moderate and severe AEs that required treatment.

In the Voluta trial, it turned out that all serious adverse events are captured within "severe adverse events." Again, there were not unanticipated adverse device effects.

And it's important to remember that we always capture the

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peak severity of an event. For example, if an event lasting 30 days was initially reported as moderate in severity and was reduced to mild after two days, in our table, the event is presented as moderate with a duration of 30 days.

There were two mild adverse events with the delayed onset. In the first case, swelling was reported almost two years following initial treatment and lasted one day. The second was a lump reported about seven months following treatment, which persisted for seven months. Both of these mild events resolved without sequelae and did not require that any action be taken, and both subjects agreed to the repeat treatment at the end of the study.

Examining adverse events that were reported as moderate in severity, we see that 44 subjects reported 70 unique moderate adverse events. All but one was injection site related. Ninety-three percent, or 65 of the 70 cases, required no treatment.

If we examine these events that did not require treatment, we see that they were all carried over from the subject diaries. So these are the same events that we discussed when I reviewed common treatment site responses. For example, if the subject reported moderate firmness which lasted more than 30 days, the event was recorded as a common treatment site response and an adverse event. As I mentioned, none of these events required treatment, and the median time to complete resolution was 38 days.

Importantly, most events were reduced to mild in severity after 9.5 days.

There were five events in four subjects which were treated with -- sorry. There were five events in four subjects which were treated with medicine or ice. Let's look at these more closely.

One subject fainted after injection and was treated with ice and smelling salts. One subject reported an ache or pain and was administered Tylenol 3 for four days. The pain was initially rated as moderate for four days and then decreased to mild, which is defined as barely noticeable, for the rest of the duration. Two subjects required treatment for lumps and bumps. Both received hyaluronidase, and the events resolved without sequelae.

Next, I'd like to present the photos of these two cases of lumps and bumps.

The 30-day photos for these subjects show that the lumps and bumps were palpable by the subject, but not visible. Of note, both subjects reported their treatment outcomes as "much improved," and one subject requested the repeat treatment at 24 months.

Looking at severe device-related adverse events, there were 12 subjects with 20 unique severe adverse events. Eighty-five percent, or 17 of the 20 events, required no treatment. If we examine these events more closely, we see that, like the moderate events, all were carried over from the subject diaries. As I mentioned, none of these events required treatment, and the median time to complete resolution was 40 days. Importantly, the

median number of days before the events were resolved or reduced to mild severity was five.

Fifteen percent, or three of the severe adverse events, required treatment. The three events occurred in two subjects. The first subject reported lumps 207 days after the last treatment. The lump was biopsied, and the report showed microscopically near normal skin with no eosinophils fills, no giant cells, a few lymphocytes and histiocytes, and mild inflammation which was not near the implant. The subject's treatment included antibiotics, steroids, and hyaluronidase.

There is a series of photos of the subject. The top series of photos were taken pre-treatment, and the bottom series represents a visit 10 months after the initial treatment, which would've captured the serious adverse event. The lump that you can see under the left eye was fluctuant, not solid, and was not part of the serious adverse event. This was discussed and confirmed with the treating investigator. The serious adverse event was in the preauricular area on the left and right side. As I mentioned, the subject was treated with antibiotics, steroids, and hyaluronidase.

The second subject reported two serious adverse events. The subject suffered a scratch from a tree branch under the left eye while playing golf, which went on to become infected and was diagnosed as cellulitis. The event progressed and the subject then reported nodularity in the right cheek area.

In the top series of photos you can see some swelling in the tear trough area. This is the site of the scratch. Treatment consisted of antibiotics, anti-inflammatories, and hyaluronidase, and the events resolved without sequelae. You can see in the bottom series of photos the event resolved.

The treatment protocol for these events followed the guidelines published by the American Society for Dermatologic Surgery, or ASDS, and commonly followed by physicians. The ASDS recommendations for treating filler adverse events include the use of hyaluronidase, antibiotics, and steroids.

Now I'd like to turn to another question posed by the Agency. The Committee is being asked to discuss the safety of Voluma as it relates to injection volume and any recommendation on maximum volume or guidelines for use. First, I'd like to review our data on the relationship between volume and safety.

Based on the results of multiple logistic regression analyses, it was also found that there was a statistically significant increase in the incidence of device-related AEs with increased injection volume and increased age.

We looked at various injection volume levels and have discussed with the Agency the possibility of placing a table similar to this one in the directions for use.

In addition, the proposed physician labeling includes a statement that common treatment site responses and adverse events may be more likely with injection volumes of 9 mL or greater.

I would also like to provide background regarding the FDA's request to discuss recommendations on volume maximums or volume guidelines.

The precaution section of the Voluma label will have a statement recommending that the maximum dose not exceed 20 mL per 60 kg of body weight mass per year. This guidance is based on preclinical studies and is consistent in methodology with other Juvéderm labeling. We look forward to the Committee's discussion on the proposed language and share the FDA's interest in receiving guidance and insights on this topic. Finally, we would like to provide additional information for the Panel's discussion on volume guidelines.

We've performed an analysis on the relationship between injection volume and response by baseline mid-face volume deficit severity. On the Y-axis we'll plot the change in mid-face volume score at Month 6, and on the X-axis we'll plot the volume injected. Any subject achieving at least a one-point change from baseline is a responder, which is represented by the black solid horizontal line. Each subject will be represented by a blue dot. For example, this dot represents a subject with moderate severity at baseline, who received a total of 7 mL of Voluma and had a two-point improvement in

the MFVDS score.

Plying the data for each subject, we can see the correlation between volume injected and change in MFVDS. These data show that the baseline MFVDS and injection volume are both related to improvement but are not the sole determinants. They also demonstrate that a wide range of injection volumes are appropriate and capable of producing a response. In other words, some subjects need more volume than others to achieve corrections even if they had the same baseline MFVDS. We believe that the directions for use should allow the healthcare provide the flexibility needed to treat each patient on an individual basis.

We'd also like to discuss our experience with Voluma outside the United States.

Results from the U.S. pivotal study are consistent with global product surveillance data on Voluma, with and without lidocaine, approved and marketed in Europe, Canada, Australia, and many other studies. With more than 520,000 syringes distributed since 2005, the adverse events that have been reported to Allergan primarily consist of reactions at the injection site, similar to those seen in the clinical study and also similar to those reported with all approved HAs.

In summary, Voluma was well tolerated by subjects. The majority of common treatment site responses and adverse events were injection site related, mild to moderate in severity, and resolved without

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treatment. There were three device-related serious adverse events in two subjects. In all cases the serious adverse events were treated and resolved. Finally, there were no unanticipated adverse device effects.

Turning now to the final discussion question from the Agency, the Agency would like the Committee to consider the appropriateness of Allergan's proposed post-approval study plans and to note any additional concerns that should be addressed.

In order to capture clinical study data on the safety of Voluma after repeat treatment, Allergan is following subjects for an additional 12 months after they undergo repeat treatment; 187 subjects are eligible for repeat treatment, 184 from the treatment group and 3 subjects from the control group who were initially treated in error; 149, or 80%, chose to receive repeat treatment, and as of the database lock, 125 subjects have actually received a repeat treatment.

Partial data on common treatment site responses based on subject diaries are already available for 120 of the 125 subjects who received the repeat treatment. The severity of these responses were similar between initial and repeat treatment, while the incidence and duration were reduced. Subjects are now being followed for an additional 12 months after repeat treatment, with a full analysis of adverse events proposed as a condition of approval.

As I mentioned earlier, in the United States the first dermal

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filler was approved in 1982, the first HA filler in 2003, and Juvéderm Ultra and Ultra Plus were approved in 2006. Voluma has been approved globally for eight years, since 2005. So there's a great deal of real world experience with HA fillers, including Voluma. HA fillers have a proven track record and are widely accepted as safe and effective.

Dr. Jones pointed out in his presentation that both measures of primary effectiveness endpoints were met. Approximately 86% of subjects with the treatment group were responders in Mid-Face Volume Deficit Scale, and the difference was statistically significant compared to the control group.

Both evaluating investigators and subjects rated the vast majority of subjects as responders on the Global Aesthetic Improvement Scale.

Finally, a key benefit of Voluma is the duration of correction that it provides the patient. The Kaplan-Meier estimates demonstrate that just over half the patients will see a clinical benefit for 21 months.

There is consistency across all primary and secondary effectiveness endpoints. Furthermore, the data are robust, as evidenced by more rigorous tests of effectiveness, such as requiring both evaluating investigators to agree on responder status or showing a mean two-point improvement on the Mid-Face Volume Deficit Scale.

In conclusion, we see that Voluma is effective for mid-face volumization. Importantly, Voluma was also well tolerated, with an

acceptable safety profile for restoring age-related mid-face volume loss, demonstrating that the benefits of treatment outweigh the risks.

Thank you for your attention, and we look forward to answering your questions.

DR. LoCICERO: I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? And please remember that the Panel may also ask questions of the Sponsor during Panel deliberations in the afternoon.

Dr. Olding.

DR. OLDING: Yes, you said in your statement that none of -- that all of the fillers for this particular study were optimized, or Voluma was optimized for injections in this particular area, and I noted that you used high and low molecular weight as opposed to regular Juvéderm.

Could you comment on why you used those two and how that optimizes it? And also could you comment about the fact that it's less cohesive and yet more hard? That seems opposite.

DR. AVELAR: Certainly. When we looked at optimizing for volumization, what we needed to do was create a material that could actually stack up, if you will, a material that could actually hold up tissue and actually elevate and lift the tissue. In contrast to the other product that you described, the Juvéderm product, which is, for instance, in the NLF, that's

meant to be a softer material that's supposed to be more malleable.

So we tried to design a material that could be injected into deeper planes, that would be more robust in terms of holding up the tissue, and that was how we started with the Voluma.

When we played with the chemistry, we found that if you take the lower molecular weight and cross-link it through a proprietary methodology, you can create a material that has different characteristics compared to Juvéderm, and it has a harder G prime, if you will, it's a harder material; and through the cross-linking efficiency, because the lower molecular weight are smaller molecules, so they can move around more randomly, and it creates a different dynamic for cross-linking. When we go through the process, the end product is a product that, for instance, if you were to inject on a tabletop, it will stack up and not necessarily collapse like the softer materials that are meant for more superficial use.

DR. LoCICERO: Yes, Dr. Ballman.

DR. BALLMAN: So you mentioned that if you use the metric that both evaluators had to classify the patient as a responder, that then it was 75.6% that were responders. Is that statistically significantly different from 70%?

DR. AVELAR: I'm going to ask our statistician to speak, please.

DR. GROSS: No. When we used that more stringent definition, the observed rate is about 75%, but the lower limit of the confidence interval,

I have to check the exact number, but it's in the high 60s, something like 67%, 68%. Obviously, the protocol was based on the average, but it does not exceed the 70% threshold.

DR. LoCICERO: Dr. Alam.

DR. ALAM: Thank you.

You mentioned that, if I recall correctly, approximately half of the injections were performed with a 25-gauge needle and about half with a 27-gauge needle.

Can you describe any patient factors or other circumstances that influence needle selection, the gauge selection, and did you find any correlation with adverse events, specifically bruising?

DR. AVELAR: So I'll answer the first component. The adverse event profile was similar for the two. And I'll ask Dr. Jones to speak to the selection and how they chose which needle.

DR. JONES: Thank you for the question. The selection was left up to the investigator. It was a 25-gauge one-inch needle or a 27-gauge half-inch needle. At my site, I prefer longer needles. I use the 25-gauge one-inch needle. Other investigators, based on personal preference, prefer a shorter needle, so it was really nothing more than that.

DR. LoCICERO: Dr. McCauley.

DR. McCAULEY: Most patients, when you treat them, have some degree of asymmetry, and I wanted to know how that was dealt with, in

terms of one side being more pronounced or needing more of Juvéderm than the other side.

And the other question I have relates to over-injection. In patients that were treated with large volumes and were over-corrected, how were they followed?

DR. AVELAR: I apologize, I didn't quite get the last part of your question.

DR. McCAULEY: How were they followed and how were they calculated in your data?

DR. AVELAR: Okay. So to the first part. The clinicians were able to treat and make their adjustment live because you can watch the volumizing as it takes place. And I'm going ask Dr. Jones to step up in a moment to address it more fully.

Your second part of your question, I apologize, it was faint with the mike and I didn't catch it.

DR. McCAULEY: Well, the second part was over-injection.

DR. AVELAR: Okay. So we did see some patients who had over-injection. In fact, in the moderate adverse events that I demonstrated, the second patient was a case of over-injection. The patient thought he felt over-injected and when he smiled he actually -- when he wasn't animating, he was fine, but when he smiled you could see some of the material. And those patients were either treated -- those patients, specifically, were treated with

hyaluronidase, but some of the other patients were fine with the way it was.

To address the asymmetry question, in terms of how that was dealt with, I'm going to ask Dr. Jones to speak to it.

DR. JONES: So you're asking how we treated asymmetry from the baseline visit, right?

DR. McCAULEY: Not only treatment, but how did you score it before treatment?

DR. JONES: How do we --

DR. McCAULEY: How were they scored before treatment?

DR. JONES: How were they scored before treatment? Okay. I believe that if there was asymmetry from side to side that was significant, we simply did not enroll them in the trial. I may need clarification on that from the study design perspective.

In terms of correcting mild asymmetry, some patients may have required more volume on one side than the other. We accounted for this in our source documentation. So basically we were documenting the amount of treatment that each individual subunit got on each side of the face. So that was documented. Moreover, we could address any asymmetry at the follow-up repeat treatment visit to correct any mild asymmetry that might persist.

DR. AVELAR: And the other part of your question, I apologize, I didn't hear the element of scoring. The overall was scored, and if there was asymmetry, the worse side or the worse zone was the score that was

attributed.

DR. LoCICERO: Just to clarify, you said that if there was significant asymmetry, they were excluded; is that correct?

DR. GROSS: Just to clarify, the asymmetry was not a formal exclusion criteria for the study. Obviously, the treating investigator needed to believe that the subject was an adequate candidate for treatment with filler in this area, but asymmetry was not called out specifically as an exclusion criteria for the study.

DR. LoCICERO: And how were they scored?

DR. GROSS: The subject receives four scores. One is overall MFVDS and then MFVDS within each of three subregions. If there was a significant difference in the severity of the two sides, the investigator was instructed to use the worst side to determine the score.

DR. LoCICERO: Dr. Miller.

DR. MILLER: Thank you for your presentation. And the question I have is, do we know why there were dropouts on the treatment side?

DR. GROSS: I'll put the slide up here. This was from the core presentation. There were 17 subjects who withdrew from the treatment group after randomization but prior to receiving treatment. Eleven of these subjects' consent was withdrawn. There were a variety of factors given. For example -- and I apologize; can we go back to the previous slide -- fear of

injection, not wanting to shave their beard off, which was a requirement of the study, for example, decided to receive other aesthetic procedures, which was a restriction within the study.

And then, in addition to the 11 that withdrew consent, there were two that were lost to follow-up. There were three where eligibility criteria were not met, but the factor that led to the exclusion was not discovered until after the subjects had been randomized.

In the control group, because there's no treatment in the control group, there really was no opportunity for subjects to withdraw after randomization but prior to treatment.

DR. LoCICERO: Dr. Ballman.

DR. BALLMAN: So of those 21 patients on the treatment group that did not have the six-month endpoint, how many were due to out of window, and how much out of window were they? And what was the window period?

DR. GROSS: So, again, I'll just put up the graphic here. So you're describing the 21 here that were in the treatment group who were missing or out of window. Let's see. We have 10 subjects who missed the Month 6 visit, that is, just did not present. They had not discontinued from the study. And we had six subjects who were out of window. The windows were contiguous between the successive study visits. So for Month 6, there was a Month 3 visit and a Month 9 visit, and so there was a window of plus or

minus 45 days.

DR. LoCICERO: Dr. McCauley has another question.

DR. GROSS: If I can just add, of those six subjects who missed the visit, one was two days early, too early, one was 12 days too late, and four of them were responders. In fact, if they are added to the analysis, they actually raise the response rate.

DR. LoCICERO: Dr. McCauley.

DR. McCAULEY: Unless I'm mistaken, I think that in your presentation you said the longevity of Juvéderm was about 21 months. That's how long you said it lasts. Well, that's how long it should last, was 21 months.

DR. AVELAR: This is the slide that we put up in terms of duration, our estimate --

DR. McCAULEY: Right.

DR. AVELAR: -- in terms of what we see with the Kaplan-Meier estimate.

DR. McCAULEY: But if you look at your treatment versus non-treatment group at six months, they had touch-ups, 80% had touch-ups. But if you look at the amount of Juvéderm injected, it was pretty much similar. It was over 6 mL. So that means to me that it was really a retreatment whereas opposed to a touch-up.

DR. AVELAR: So it would be six months from the touch-up,

from the last touch-up.

DR. McCAULEY: Right.

DR. AVELAR: And to get a sense of volumes, that may be helpful. The first visit was meant to under-correct the patient, try to get them to an optimal but not over-correct them. So it was a conservative approach. And the average patient there got approximately 5.2 cc. The patient then returned one month later for a follow-up, and they were eligible for a touch-up to address, for instance, any asymmetries or to address if that patient needed to be further optimized. On average there, of the patients who had it, they got about 2 mL, and that rounds up to a total of about 6.8. Eighty percent of patients got it. The endpoint that's used is as of the last treatment, so it would be after the last injection.

DR. McCAULEY: If I'm not mistaken, your slide said 6.6 for the treatment group and 6.6 also for the non-treatment group.

DR. AVELAR: Perhaps we can put up the slide of the discussion from the core slide.

DR. McCAULEY: Yeah. And were there any distinguishing characteristics of the 20% that did not receive the touch-up at six months?

DR. GROSS: Okay. So just to make sure I can clarify your question. So, yes, 82% of the subjects did receive the optional touch-up treatment. And so you're asking if there are any unique characteristics of the 18% that did not receive the optional touch-up treatment?

DR. McCAULEY: Right.

DR. GROSS: Yeah, we'll have to see if we can find some --

DR. AVELAR: The simple answer is the clinician, at the one-month mark, felt that that patient had been optimized and didn't need any further injection.

DR. ALAM: May I ask a question, a follow-up to that?

DR. LoCICERO: Dr. Alam.

DR. ALAM: With regard to the issue of longevity to which the previous Panel member was asking, I think in your graph you had a plot, the Kaplan-Meier plot showing the diminution in response, and I think it was up to 21 or 24 months and then it was -- so there was a dotted line going down to the zero mark.

Given that the effectiveness towards the end of the solid line was about 40%, I'm assuming the controls have the consistent response of about 39%. Would you say that that is the point at which the clinically significant result could be said to come to an end because it would be crossing the control line?

And a related question to that would be, given that three of the control subjects were apparently misclassified and received treatment, if you remove those misclassified subjects from your data and reanalyze it, how much does the response rate for control subjects diminish significantly less than the 39% that you told us?

DR. AVELAR: I don't know that we've taken them out completely, but if you remove the two, it drops from 39% to about 29%. If we would move them over.

And then, to the first part of your question, do you want to address that?

DR. GROSS: So the Kaplan-Meier estimates could reasonably be compared to the control group response across time. We actually only have control group response rate estimated at Month 6. That was the point at which the control group then received treatment. So under an assumption that that rate remains constant over time, the 45% would likely not be statistically significantly greater than 40% at the Month 24 time frame. Yeah.

And to clarify, certainly the median duration has often been proposed as a good marker for what would be considered the duration of use. So that median is at 21 months. And so we would be certainly comfortable with a conclusion that, at 24 months, is also not significantly different.

DR. ALAM: I suppose it's possible that the 45% would be distinct from the 28% if you removed the control subjects. I don't think you did that analysis.

DR. GROSS: Well, we didn't. I'm sorry. We actually did analyze the primary analysis using an as-treated methodology.

DR. ALAM: Yes, yes.

DR. GROSS: And as Dr. Avelar mentioned, what that does is it lowers the control group response because, in an as-randomized analysis, we have three subjects --

DR. ALAM: Right.

DR. GROSS: -- who received treatment.

DR. ALAM: Thank you.

DR. LoCICERO: Dr. Olding.

DR. OLDING: I just have a question about the exclusionary criteria, thin skin, tendency to accumulate fluid in the lower eyelids, and the large infraorbital fat pads. Many of us inject, off label, HAs in the areas that we've discussed and we're talking about today, and if I excluded those people in my patient list, I exclude about 25% of the people that I inject, perhaps a little bit more.

I'm curious why you excluded particularly the thin-skin people. This is something that we're injecting at a deeper level. So, theoretically, whether or not you have thin skin should not make any difference, unless this tends to be lumpier or bumpier than the other things that we inject. So I'd just like you to comment on that.

DR. AVELAR: Sir, you're correct, the injection plane is much deeper. But what we were trying to do in the study was to limit confounding variables. And we also recognize that patients with thin skin had at least a theoretical potential to accumulate more fluid, and we weren't sure if it

would become a confounder, so we elected to exclude them in this trial.

DR. OLDING: So you said that people who had thin skin tend to accumulate more fluid?

DR. AVELAR: Or have the propensity or the --

DR. OLDING: Why would you do that?

DR. AVELAR: Actually, if I can ask Dr. Jones to speak to that. He was involved in this process.

DR. JONES: The decision to include the people with thin skin really sort of grew out of the issue of the problems that we see in the tear trough. So thin skin, as you might find in the tear trough, most patients don't have that in clinical practice. Perhaps some very elderly patients. But it was decided to exclude the tear trough altogether from the treatment site in patients who may have exceedingly thin skin, such as skin that you may find in the tear trough area.

So this exclusion criteria was sort of borne out of concerns of our experience with treating the tear trough with fillers that are too robust, if you will.

DR. OLDING: Well, I agree, and I think that area in particular is difficult to treat no matter what HA you use, because there is a greater possibility of having lumpiness in that area. Are you then saying, because that is part of the malar area, that you should not be injecting that portion of the malar at all with this product?

DR. JONES: Yes, that part of the malar area, the tear trough, was specifically excluded from the injection site.

DR. OLDING: Because, depending on what you define as the tear trough level or tear trough area, in everyone it's very thin. The very proximal part of the tear trough is very thin in every patient, so I don't really understand.

DR. JONES: I could show you a diagram, if we could pull that up, of the treatment area. Let's see if we are able to get that. But the concept, if we take a look at this slide, you can see, the superior line there was avoiding that superior medial aspect of the tear trough where the skin is the thinnest. So the superior border was where we were instructed to stop our treatment. And particularly we wanted to be not too far above any retaining ligaments there and into the tear trough per se, where that thin skin is.

DR. OLDING: So if you disregard that area, we're really not talking about that area, you're talking about thin skin over the malar area, which is something different.

DR. JONES: Correct, thin skin within the predefined treatment zones.

DR. OLDING: And why did you then exclude that area in the predefined treatment zones?

DR. JONES: Why did we exclude thin skin?

DR. OLDING: Um-hum.

DR. JONES: Okay. The thinking was, if there was very thin skin such as the skin that you may find in the tear trough, we did not want excess swelling there. I can tell you that, in screening these patients, the issue really did not come up.

DR. LoCICERO: Okay, Dr. Chevray.

DR. CHEVRAY: Yes, I have a question that relates to the determination of the effectiveness of Voluma. The no-treatment control group, as you mentioned, the 39% response rate, which was a bit surprising to me -- and I don't conduct these kinds of studies, but specifically I have a question about the selection of the control group.

Why was a no-treatment control group selected? So that does not control for injection trauma of placing some sort of material within tissues, which could cause internal scarring and actually cause a response. Was there some impediment to creating a double-blinded study where you would have a sham injection or injection vehicle or something like that?

DR. GROSS: Certainly a control group, an active control group, as you described, that could've had an injection of a sham such as saline, would've been a very good idea. It provides for a more active control. In our discussions with the FDA, given that there was no product approved at the time, we didn't have a legitimate control, for lack of a term, or a control that we could've used on label. So, in retrospect, certainly a control that had an

active, such as a sham injection, would've been better.

We did follow the precedent that was set with, for instance, the Restylane product that just went through the Panel. They had the same situation as we had, in that there was no product on label, so they elected and through discussions with the FDA settled on a non-treatment control.

DR. LoCICERO: So let's continue with control group questions. Slide C-43. This is interesting, in that the evaluators of the control group are the same ones who evaluated the treatment group. And the standard deviation, although not statistically different, is quite large.

Is there an explanation why the evaluators had such a significant problem in evaluating the control group? And can you also speak to their training in the use of the photometric volume deficit scale?

DR. AVELAR: I'll ask Dr. Gross.

DR. GROSS: So if I may take the training question first. All of the investigators in the study went through extensive qualification in the use of the scale. This was the treating investigators who used the scale to qualify the subjects to an eligibility. And the evaluating investigators, they went through a series of teleconferences to be trained on the use of the scale, and then they went through a series of ratings of subject images in two rounds separated by a minimum of two weeks. Each of the investigators had to demonstrate adequate intra-rater reliability, that is, agreeing with their own ratings over time, and could not deviate from any individual other rater in the

study. So they had to actually meet the .6 threshold in terms of inter-rater agreement with every other rater within the qualification study. So on the basis of that, they were training qualified in the use of the scale.

As for the standard deviation -- and this is a dichotomous outcome. So what you're seeing here in the error bars is really a function of the fact that the control group response is closer to .5. I mean, that's just an artifact of the statistical technique that is used.

But you also were asking about the evaluators' ability to rate control subjects versus their ability to rate treatment subjects. The treatment subjects very often had a clinical response. So if we look at the amount of change, the treatment subjects very often had a greater than one-point change.

We showed this slide during the core as well. This is a look at how the response rates change as we raise the threshold that defines a responder. Only one-fifth of the treatment group responders had a one-point change. Four-fifths of them had a greater than one-point change. However, half of the control group responders had a one-point change.

So what you're seeing is really the subjective scale. There is some possibility that when you make an absolute rating at Month 6, that it may be different from the absolute rating given to that subject at baseline. If it differs by one point for both evaluating investigators, then that subject would be deemed a responder. And that did happen in 38% of the control

group.

DR. BALLMAN: Just for clarification on that, if you go back to the other slide and we look at the error bar, is that a standard error of the estimate? And if so, wouldn't the sample size also explain why that's bigger?

DR. GROSS: That is actually a confidence interval. That's the 95% confidence interval.

DR. BALLMAN: Right. But still, that would be driven by the sample size, right? So you would expect a wider confidence interval for that control group because you only had 40-some people in it.

DR. GROSS: Yes, obviously it's a baseline dichotomous outcome --

DR. BALLMAN: Right.

DR. GROSS: -- which doesn't have as direct of an effect on sample size. I'd say a mean, a confidence interval around the mean, would. But it certainly gives a function of sample size; you're absolutely right.

Thank you.

DR. LoCICERO: Dr. Alam.

DR. ALAM: Thank you.

I have a question about the adverse event list, and if I read it correctly, there is a mention of discoloration on the list. I was wondering, discoloration, is that defined to include such things as hyperpigmentation, hypopigmentation, possibly even bruising in selected cases? And how did you

define that both for the investigators and for the patients, if they would self-report?

Thank you.

DR. AVELAR: So the discoloration was recorded by the subjects in the subject diaries. And so yes, they can describe hypo- or hyperpigmentation. We didn't see that in the clinical trial. The bulk of the discoloration was either a branching or, moreover, for the most common reason, it was actually almost like hemosiderin stain after.

We looked at the discoloration, and it's interesting. Of the 109 patients who demonstrated some bruising, 100 had the discoloration, and the temporal association of the discoloration almost always goes away within the course of a few weeks. Certainly within the month. So it was left to the subject what discoloration meant.

DR. LoCICERO: Dr. Miller will ask the last question for the session.

DR. MILLER: Thank you.

Was the mid-face volume deficiency scale developed for the purpose of this study or is that -- did you use that? That was developed elsewhere?

DR. AVELAR: It was developed for the purpose of the study.

DR. LoCICERO: Okay, let's take a 15-minute break. Panel members, please do not discuss the meeting topic during the break amongst

yourselves or with any member of the audience. We will resume at 10:15.

(Off the record.)

(On the record.)

DR. LoCICERO: The FDA will now give their presentation on this issue.

Joseph Nielsen, you may begin.

DR. NIELSEN: Good morning, everyone. My name is Joe Nielsen, and I'm a biologist in the Division of Surgical Devices in the Center for Devices and Radiological Health, and the lead reviewer and one of the preclinical reviewers for Allergan's Juvéderm Voluma XC premarket approval submission.

The Juvéderm Voluma XC PMA submission was reviewed by the Plastics and Reconstructive Surgery Branch, and the review team includes the following CDRH and CDER members.

Janette Alexander conducted the clinical review. Alvin Van Orden conducted the statistical review. Lauren Min conducted the epidemiology review. Dave Kaplan and Irada Isayeva conducted the chemistry review. Ying Wang conducted the lidocaine drug master file review. Irfan Khan conducted the bioresearch monitoring review. George Ngatha conducted the GMP review. Anna Staton conducted the patient labeling review. Charles Durfor is the IDE lead reviewer. And David Krause and Jiyoun Dang are PRSB1 and 2 branch chiefs.

So I will begin the FDA presentation with a brief introduction including the device description, the rationale for bringing the Voluma XC to this Advisory Panel meeting, and an overview of the preclinical testing submitted by Allergan in support of this PMA. My presentation will be followed by Dr. Alexander, who will present FDA's review of the Juvéderm Voluma XC clinical study. Alvin Van Orden will present FDA's review of the statistical analysis. Dr. Min will present FDA's review of the proposed post-approval study. And the FDA presentation will conclude with Panel questions and FDA summation.

So as we've heard, Juvéderm Voluma XC is a biodegradable dermal filler. It's formulated from a mixture of low and high molecular weight hyaluronic acid and contains .3% lidocaine in phosphate buffered saline. The hyaluronic acid is cross-linked with 1,4-butanediol diglycidyl ether forming a hyaluronic acid gel and is packaged and sterilized in 1 mL syringes and delivered with 27- or 25-gauge needles.

Although hyaluronic acid is not a novel material for dermal fillers, Juvéderm Voluma XC is a new HA formulation when compared to the approved Juvéderm products.

Key differences include the mixture of low and high molecular weight HA, low HA concentration, use of less cross-linker, and different rheological properties, including an increase in elasticity.

Key similarities include the same lidocaine concentration,

degradation mechanisms, residual cross-linker specification, and pH and similar extrusion force range.

Juvéderm Voluma XC was brought to this Advisory Panel because Allergan is seeking a first-of-a-kind mid-face indication. Juvéderm Voluma XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face. In addition, this product is a new HA material formulation, typically requires increased injection volumes for the mid-face indication, and has a prolonged resorption profile.

Juvéderm Voluma XC was evaluated with in vitro and in vivo biocompatibility studies. The biocompatibility studies were performed in accordance with good laboratory practice regulations, ISO 10993 test methods, and FDA's G95-1 Blue Book Memorandum.

The following preclinical studies were reviewed by FDA. Juvéderm Voluma XC was not cytotoxic, was not a sensitizer, and did not cause systemic toxicity in biocompatibility studies.

The initial three-day irritation test reported moderate to severe erythema over the course of the study. Irritation testing was repeated in a 14-day study using approved dermal fillers as controls. The repeat study demonstrated that the irritation response elicited by Juvéderm Voluma XC was similar in magnitude and duration as the approved dermal filler products, and response declined to a minimal level in approximately three to four days.

Juvéderm Voluma XC did not cause toxicity in a 13-week sub-chronic study conducted for ISO 10993 Part 11, and did not cause irritation or inflammation in 4- and 12-week muscle implantation studies conducted per ISO 10993 Part 6. Voluma XC was non-pyrogenic in a rabbit material-mediated pyrogenicity assay conducted per USP <151> and meets product endotoxin release specifications in testing conducted per USP <85> and <161>.

Voluma XC did not cause genotoxicity in a bacterial reverse mutation assay, chromosomal aberration assay, or mouse peripheral blood micronucleus assay. This is an appropriate panel of short-term genotoxicity studies and meets the extent of FDA's recognition of ISO 10993 Part 3.

The cancer risk of the BDDE cross-linker is adequately mitigated with the negative genotoxicity testing results, BDDE purity specifications, and the cancer risk assessment. The calculated excess cancer risk from residual BDDE exposure ranged from 6.1×10^{-5} to 1.6×10^{-8} . These values represent the probability of developing cancer due to BDDE exposure and are in the same negligible range as previously approved BDDE-containing products.

Key material specification and characterization testing included pH, extrusion force, rheology, cross-linking efficiency, degradation, free HA content, hyaluronic acid and lidocaine concentration and lidocaine diffusion studies. Juvéderm Voluma XC meets all product specifications.

Filled syringes are sterilized with a validated moist heat

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process. The sterilization cycle is validated according to the FDA-recognized sterilization standard ISO 17665 Part 1 and provides a minimum Sterility Assurance Level of 10^{-6} . Acceptable stability data has been collected through 24 months.

FDA concludes that preclinical testing provides a reasonable assurance that the Juvéderm Voluma XC product will be biocompatible and that all identified toxicity risks have been adequately mitigated.

So with that preclinical summary, I would like to introduce our medical officer, Dr. Alexander.

DR. ALEXANDER: Good morning. My name is Janette Alexander. I'm board certified in plastic surgery, and I'm the clinical reviewer for this premarket application. This morning I'll present the clinical overview of Juvéderm Voluma XC for cheek augmentation.

The original Juvéderm product was approved under PMA P050047 in 2006 for mid- to deep-dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Allergan has now completed studies of a new material, known as Juvéderm Voluma XC, in support of a request for an indication for cheek augmentation.

Voluma XC for cheek augmentation is presented for Panel discussion because cheek augmentation is a first-of-a-kind indication for use. It is to be administered in the deep subcutaneous and/or supraperiosteal plane as opposed to the dermal plane. A pivotal study was performed to

evaluate the safety and effectiveness in the augmentation of the cheek to correct age-related volume deficit in the mid-face.

Voluma XC is a new formulation of hyaluronic acid and includes both high and low molecular weight material. The Sponsor developed this formulation to increase viscosity and elasticity.

An open-label Australian pilot study was done to evaluate durability of Voluma XC in cheek augmentation. Safety data were collected by diary, and patients were followed for 24 months. Entry criteria and patient demographics were similar to the present pivotal study; 103 subjects were enrolled and 72 completed the study. The total mean volume injected was 5.1 cc, given in two treatment sessions that were separated by four weeks.

Unblinded assessments using the Sponsor's Mid-Face Volume Deficit Scale were done with the primary assessment at Week 8. Although unblinded, it was felt that 82% of patients at Week 78, or 18 months, were still responders.

Voluma and Voluma XC are marketed outside the U.S. More than 520,000 syringes have been distributed worldwide. International postmarket surveillance identifies the same types of common treatment responses and adverse events as reported in the U.S. clinical study.

Study VOLUMA-002 was a randomized, evaluator-blinded, no-treatment control study of the effectiveness and safety of Juvéderm

Voluma XC in the augmentation of the mid-face for age-related volume deficit. The no-treatment patients were treated with Voluma XC at six months.

The primary effectiveness endpoint was the average of two blinded evaluators' assessments of the overall mid-face volume using the Mid-Face Volume Deficit Scale at six months. A responder is defined as a change of 1 or more on the Mid-Face Volume Deficit Scale. Treatment success was defined as at least 70% of patients assessed to be responders, in addition to a statistically superior difference from the control.

Secondary and additional effectiveness endpoints included the evaluator-investigator Global Aesthetic Improvement Scale assessment, overall and by facial region, and 3D volume calculations. Mid-Face Volume Deficit Scale assessments for each treatment area were also evaluated by the evaluating investigator.

Patients utilized the Global Aesthetic Improvement Scale for assessments, which were compared to evaluator Global Aesthetic Improvement Scale scores, as well as self-rated MFVDS scores which were compared to the investigator scores. Multiple patient-reported outcome questionnaires were included.

Mid-Face Volume Deficit Scale is a six-point scale. Both descriptive narration and photos were provided to the evaluating investigators. Patient inclusion criteria included a score of 3, 4, or 5,

corresponding to moderate, significant, or severe deficit, for enrollment in the study.

As you've seen previously, this is a photograph of the scale. Twelve patients are represented in three angles. The photoscale and narrative descriptions were used as reference for live, blinded evaluations.

Three subregions were evaluated secondarily, the zygomaticomalar, the anteromedial cheek, and the submalar region.

The primary safety endpoints were the adverse outcomes during the first 30 days and the adverse events reported by the investigators at all time points.

299 patients were randomized in a 5:1 ratio. There were 30 non-randomized run-in patients, two at each site, to familiarize the treating investigators with the device and injection techniques. The study then consisted of 235 immediate-treatment patients and 47 no-treatment controls.

Subjects were enrolled at 15 investigational centers by 15 investigators. Baseline assessments were performed by the blinded investigators. Treatment group patients were evaluated at 72 hours by phone or e-mail, and at one, three, and six months, and then every three months to a total of 24 months. No-treatment controls followed this schedule until six months; then they received treatment and followed a similar schedule. Touch-up treatments were provided at four weeks post-

treatment if required to achieve optimal correction.

Subjects completed a 30-day post-treatment diary after each injection. The treating investigator assessed safety outcomes at each visit, and the blinded evaluators performed Mid-Face Volume Deficit Scale and Global Aesthetic Improvement Scale evaluations at each visit, beginning at one month post-treatment. Photographs were obtained at each visit.

All subjects were offered repeat treatment anytime after the 12-month visit, if the evaluators' scores returned to baseline, or at 24 months, if not already given. Touch-up treatments were not provided after a repeat treatment. Follow-up after repeat treatment continues to 12 months.

All patients received a small subcutaneous injection in the postauricular space or the upper inner arm. A subset of 36 volunteer patients were randomized to have a biopsy performed at one of nine follow-up visits; 21 biopsies were obtained.

The implant was absent in two-thirds of samples. Mild inflammation was present in nearly all samples, and mild to moderate fibrosis was present in three-quarters.

Demographics included a mean age of 54 years, with a range of 35 to 65. Most patients were female and white.

The study included 124 Fitzpatrick Type IV to VI patients. There were 57 Type IV, 53 Type V, and 14 Type VI patients in the study. Fifty-six men were included.

Of the treatment group of 235, 208 were evaluable at the six-month primary endpoint; 174 completed the extended follow-up. In the control group of 47 patients, 3 were treated in error at the beginning of the study, 32 were treated as intended at six months, and 29 remained in the study at 18 months; 125 of the 184 patients who were offered repeat treatment as of the database lock chose to have the repeat treatment.

Twenty-one patients had missing or out-of-window six-month assessments. Sixty-one patients did not complete the extended follow-up, and the main reasons were that they withdrew consent or were lost to follow-up.

Mean total volume injected in the initial treatment and touch-up sessions combined was 6.79 cc per patient, with a range of 1.2 cc to 13.9 cc. Repeat treatment volume was much smaller, 2.5 cc on average. Device implantation was achieved by subcutaneous and/or supraperiosteal injection in all patients. The majority of patients received a combination of injection methods, such as tunneling, linear retrograde, linear antegrade, and serial puncture. Most patients received an anesthetic, either topical or injected locally or regionally or both. Two-thirds of patients received an anesthetic for any injection session. This did not change for subsequent treatments.

The primary endpoint assessment is the blinded, live assessment with no knowledge of treatment group. After six months, all

patients were treated, so the benefits of blinding are lost for subsequent visits. The blinded evaluators, however, did not have any knowledge of volume or area injected.

In the treatment group, more than 85% were determined to be responders by the blinded evaluators. In the no-treatment group, 39% were considered responders. The study met the pre-specified primary effectiveness criterion of 70% responders and was 47% greater than the no-treatment group.

Secondary endpoints included Mid-Face Volume Deficit Scale assessments for each treatment area, and additional endpoints included the blinded investigators' assessment with the Global Aesthetic Improvement Scale as well as 3D photo volume determinations.

The mid-facial region responder ratings were similar to the overall rating.

The Mid-Face Volume Deficit Scale is a validated scale. The Global Aesthetic Improvement Scale is an unvalidated scale, but one which is used to reflect the patient's assessment of change. It is difficult to quantify aesthetic change, and this may be reflected here, as the untrained and unblinded patient did not reach the same conclusions as the investigators using the validated scale, although they appear to largely believe they were improved on a more subjective scale.

The patient assessments remain fairly constant, in the 50% to

60% range, as opposed to the investigators, who were trained and had a decrease in assessment over time. However, the patient global assessment of whether they were improved or much improved corresponded to the initial more beneficial number and then decreased over time.

The Mid-Face Volume Deficit Scale was validated, and investigators were trained in its use. Multiple training sessions and testing were required to achieve acceptable reliability by all investigators.

We would appreciate the Panel's input on clinical utility of photo scales and other possible methods to evaluate aesthetic outcomes.

Safety assessments included adverse events and common treatment responses. The majority of the common treatment responses resolved by 60 days. The five most common treatment responses lasting more than 30 days, which were then classified as adverse events, were mass, induration, swelling, pain, and discoloration.

Common treatment responses included tenderness, swelling, firmness, lumps and bumps, bruising, pain, redness, discoloration, and itching.

Factors associated with a higher incidence of common treatment responses were found to be age, volume injected, and a tunneling technique.

The majority of common treatment responses were moderate in severity, as can be seen in this slide. Moderate severity is defined as

sufficient severity to make the subject uncomfortable and to influence daily activity.

Adverse events are defined in several ways. They are categorized by severity: mild, moderate, or severe. They are also separated into serious adverse events, which include death and disability or substantial disruption of normal life functions, or need for medical or surgical intervention to prevent all of the above.

Thirty-three percent of patients had device- or injection-related adverse events. The majority of these adverse events were mild or moderate in severity, with 15 subjects experiencing 20 severe adverse events which were either device or procedure related. Of the severe adverse events, two patients had three events that were also classified as serious adverse events.

A decrease in incidence of adverse events was seen with repeat treatment. This decrease is consistent with what we've seen in previously approved fillers and may also reflect the lower volume used for repeat treatment.

There were five patients who had late-onset adverse events, three of which were severe and required intervention.

This is a list of the 15 patients who had severe adverse events at any time in the study, which were definitely, probably, or possibly related, and all are localized to the treatment area. Twelve of these lasted longer than 30 days, and all were related to firmness, lumps or bumps.

Eleven patients experienced serious adverse events. Three of these serious adverse events were classified as device related and occurred in two patients. They were all nodularity which developed more than six months post-treatment.

It is of interest that although the number is quite small, there are serious adverse events that develop many months after injection. We would like you to consider the relevance of these adverse events, if any.

One death occurred. The patient was a 64-year-old Hispanic male who received a single treatment session with a total volume of 7 cc injected. One year after injection he developed a stroke, was hospitalized, and subsequently died.

A second patient of interest is a 60-year-old white female who received an initial injection of 6 cc. Eight months post-treatment she noted a change in her vision. She was evaluated by ophthalmology and neuro-ophthalmology with a diagnosis of optic neuropathy. Workup included carotid doppler, MRA, MRI, which revealed normal carotid flow with mild plaque in a doppler study, and an MRI which documented presence of presumed filler in the facial region injected without other abnormality. She was also noted to have an asymmetric visual field defect in the opposite eye, which she had not noticed. And etiology is unclear. The patient received an additional injection of 6 cc at 12 months without further sequelae. FDA cannot definitively conclude that this adverse event is not device related.

Next, I'll show you the photos of patients with serious adverse events.

This is a 60-year-old white female who received 2.5 cc of Voluma XC in December of 2009, with a touch-up of 1.25 cc one month later. She developed masses in both cheeks seven months after the last treatment. She was treated with antibiotics, anti-inflammatories, and hyaluronidase in nine sites. She discontinued the study due to the adverse event.

This is a 60-year-old white male who received 11.3 cc of Voluma XC in March of 2010. Inflammation developed under the left eye six months after treatment and nodularity in the right cheek seven months after treatment. He was treated with topical steroids, antibiotics, anti-inflammatories, and hyaluronidase, with resolution of the masses and inflammation.

We'll now examine the relationship of injection volume to adverse events.

The protocol specified a maximum total volume of 12 cc for initial plus touch-up and 12 cc at repeat treatment. The average volume for initial injection plus touch-up was a total of 6.79 cc. The range given was 1.2 cc to 13.9 cc. Repeat treatment volume average was 2.56 cc.

This chart shows the relation between adverse events and volume. We would like to ask you to discuss the relationship between increased volume and incidence in severity of adverse events and to

comment on the recommended volume maximums or guidelines. Please note that the responder rate also correlated to volume, with a 74% rate over 6.5 cc injected and a 96% rate -- excuse me -- a 74% rate less than 6.5 cc and a 96% rate greater than 6.5 cc.

Now I'll show you some photos. The next two slides are typical outcomes that were considered.

This is a 49-year-old Hispanic female who received 6.9 cc. Her Mid-Face Volume Deficit Score decreased from 4.5 to 3 at 6 months. She assessed herself to be unchanged at six months using the Global Aesthetic Improvement Scale.

This is a 57-year-old white male who received an initial injection of 4.55 cc followed by a touch-up of 2 cc. His self-assessment at six months was "mildly improved," while his Mid-Face Volume Deficit Score by evaluating physicians decreased from 3 to 1.5.

The next two photos were chosen by the Sponsor as some of the worst effectiveness outcomes.

This is a 58-year-old black female who was treated with initial and touch-up total volume of 4.7 cc of Voluma XC. Her Mid-Face Volume Deficit Scale score at six months remained unchanged at 3. Her global aesthetic improvement score by self-assessment was "mildly improved."

This is a 52-year-old white female who had treatment with 3.8 cc of Voluma XC in initial and touch-up sessions. Her Mid-Face Volume

Deficit Scale score at six months was unchanged at 3. She also felt herself to be mildly improved using the self-assessed Global Aesthetic Improvement Scale.

Next are the photographs of some severe adverse events.

This is a 64-year-old white female who had initial plus touch-up treatment with 11.1 cc. She had severe firmness which persisted for 69 days. She had retreatment at 27 months when offered, despite experiencing the severe adverse event.

This is a 61-year-old white female who received 5.4 cc in initial plus touch-up injections. She experienced severe firmness, lumps and bumps which lasted 40 and 36 days. Her self-assessment at six months was "mildly improved."

So over 78% of subjects had adverse outcomes that they felt affected their daily activity or were disabling. The majority of these resolved in less than 30 days. Twenty percent of patients experienced prolonged effects that mainly consisted of firmness, lumps and bumps. A few patients developed late-onset adverse events, again lumps and bumps that occasionally required intervention.

The benefits and risks are weighted to determine appropriateness of use for a device. You will be asked to consider all aspects of the patient outcomes to address device safety and effectiveness.

In summary, the study met its primary endpoint and was

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supported by its secondary and additional endpoints.

Common treatment responses were mainly moderate in severity and related to firmness, lumps and bumps. But 20% of patients had events lasting more than 30 days.

The safety profile appears to be similar to other hyaluronic acid fillers, except for the duration of firmness, lumps and bumps, and the occurrence of a small number of late-onset adverse events.

FDA would appreciate your comments regarding useful tools for clinical evaluation of effectiveness and assessment of the safety profile, in particular the relationship of volume injected to adverse events, the duration of adverse events, and the occurrence of late adverse events.

This concludes the clinical presentation. Thank you for your attention.

MR. VAN ORDEN: Hi, my name is Alvin Van Orden, and I'm the statistical reviewer for this PMA.

Let me begin by reiterating that a responder is defined as a one-point change on the Mid-Face Volume Deficit Score, or MFVDS. For the study to be considered a success, the treated group had to perform significantly better than the no-treatment control and significantly better than the 70%.

The secondary endpoint was the Global Aesthetic Improvement Scale, and the additional endpoints I will discuss are patient satisfaction,

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evaluation of other time points, and the imaging data.

Each subject was evaluated by two evaluators that were blinded to the treatment assignment. In this table we see the amount of time the two evaluators agreed in their assessment of the subject. All of the times the two evaluators agreed will be on the diagonal, and because the ratings have been sorted by highest to lowest, no observations will appear below the diagonal.

You'll notice that there were instances where the two evaluators differed by as many as four points out of a possible five, where one evaluator rated the subject as a five (severe) and the other rated the subject as a one (minimal). There was exact agreement between the two evaluators only 41% of the time, and of 15% of cases the two evaluations differed by two or more.

The MFVDS was validated before the study, and the evaluators underwent a strict training. The weighted kappa based on overall MFVDS blinded evaluations between zero and six months is 0.65, which is a reasonable level of agreement. In the MFVDS evaluations for subregions and in overall MFVDS evaluations after six months, there was less observed agreement in the evaluations.

So for a one-point change, a one-point difference on the MFVDS as a meaningful difference, then there was a meaningful difference in the two evaluations more than half the time. It is unclear if a one-point

change on the MFVDS is an appropriate definition of a responder, and the Panel will be asked to comment on the appropriateness of the primary endpoint as a measure of mid-face volume.

Because of the lack of agreement in the MFVDS, the FDA asked the Sponsor to perform two responder analyses, the pre-specified one where a responder is defined as a one-point change, and another where a responder is defined as a two-point change.

In the pre-specified analysis, the Sponsor clearly met the primary endpoint, as a responder rate of 86% was significantly better than both the no-treatment control and the 70% level that was designated. When responders were defined as having a two-point change, the treatment group was still significantly better than the no-treatment control. The run-in subjects and the subjects in the control group that received a late treatment after six months showed very similar levels of effectiveness to the main treatment cohort.

And at this point I'd also like to make a small clarification to what was said earlier this morning. In talking with the Sponsor, they have agreed that there were three subjects that were treated from the control group. Only two of those had six-month visits that are included in these numbers. And so the control group response rate for a one-point change is 35% if you take those out. So still very similar.

Given this understanding of the results, we'll backtrack and talk

about subject accounting.

329 subjects were eligible; 30y were run-in subjects that all received treatment and were not randomized; 17 were randomized to the treatment but dropped out of the study before receiving treatment. 282 subjects began the study, with 235 in the treatment group and 47 in the control. Not surprisingly, the control group had a higher dropout rate, as they were not offered treatment until six months; 11% of treatment subjects and 24% of control subjects were not included in the primary analysis. Overall, 13% of study subjects did not have a six-month evaluation.

We looked at different methods of analyzing missing data, including the worst-case scenario. But even when all missing treated subjects are considered non-responders and all missing control subjects are considered responders, the treatment group is still significantly better than the no-treatment control.

For the secondary endpoint of overall aesthetic improvement, the evaluating investigators were given baseline photos of the subject and asked to rate each subject as much improved, improved, no change, worse, or much worse.

I should mention that though this is a commonly used endpoint, this is not a validated endpoint.

But at six months, 82% of treated subjects were rated as being either improved or much improved, as compared to 22% of the control

subjects.

Subjects were allowed to rate themselves on the MFVDS, and based on their ratings, 58% of treated subjects would be considered responders. It is not clear if the lower response rate is due to the lack of training on the MFVDS or if the perceived change is less than one point on the MFVDS scale.

Subjects were asked to rate their satisfaction with their own appearance on a scale where zero equals not at all satisfied and four equals completely satisfied. And about 90% of treated subjects increased in their level of satisfaction in at least one of the regions, though very few were completely satisfied.

Surprisingly, unblinded control subjects also increased in satisfaction, such that the difference in the change in satisfaction between the two groups was about a half point for most regions, though there was no difference in the average amount of satisfaction for the area under the lower eyelids.

Eighty percent of subjects that were eligible for retreatment accepted the retreatment, indicating that most subjects that reached the 24-month endpoint saw a positive benefit-to-risk ratio. And if one assumes that subjects that were lost to follow-up would've declined treatment, then approximately 60% of subjects accepted retreatment.

Over time the effectiveness of the device tapered off. Of

subjects that reached the two-year endpoint, 67% were still considered responders. Factoring in the loss to follow up, the Sponsor estimates a 45% probability of being a responder after two years. However, after six months there is no control group for comparison and the evaluating investigators were unblinded, so evaluations may be biased.

The Panel will be asked to comment on the validity of long-term effectiveness claims.

At each visit advanced 3D imaging techniques were used to calculate the change in volume over the course of the study. This table reflects only those subjects that had imaging results at all of the time points shown in this table. If a subject was considered not to be a responder at one visit, then imaging data would not be collected at the next visit. Consequently, of these treated 113 subjects, 73% were responders at 24 months.

Still, the imaging data does not reflect the same decline in appearance that was reported by the evaluators. For the same treatment subjects, the average change from baseline in the MFVDS score still declined over time from 1.9 at 6 months, 1.75 at 12 months, and 1.2 at 24 months. On the other hand, the imaging volume stays relatively constant from 6 to 24 months.

Another curious note is that average change in volume for both treated and control groups was larger than the volume injected. While the

exactness of the photographic measurements is questioned, it is clear that the treated subjects had significantly higher imaging volumes than did the no-treatment control subjects, which is supportive of the overall claim of effectiveness.

It remains unclear how to resolve differences between photographic volumes and evaluations of investigators, and it is unclear how photographic evidence should be used in similar studies going forward. And we invite comments from the panelists.

There were highly significant differences in effectiveness between the 15 sites in the study. It should be noted that we are unable to distinguish between differences among treating investigators and differences between evaluating investigators, as evaluations were performed live at each site. We were not able to detect a treatment by site interaction, but keep in mind that there was a 5:1 randomization ratio, so there are very few control subjects at each site, making it difficult to test for treatment by site interaction.

The responder rate for the MFVDS ranged from as little as 13% to as high as 100%. The median imaging volume did not show a consistent relationship to the injected volume, and the device-related adverse event rates ranged from 13% to 60%. In short, the level of risk and benefit of treatment can depend heavily on the site, even in the trained, controlled environment of a clinical study.

Common treatment responses are expected events that last less than 30 days. And we saw trends for increased discoloration, bruising, and itching as age increased, and we saw trends for increased swelling and bruising as greater volumes were injected. We did not see additional risks for darker skin types.

If CTRs persisted longer than 30 days, they were considered adverse events, and we created a logistic model of incidence of device-related adverse events to see what covariates might be important in predicting adverse events. We found age and volume to be highly significant predictors, with increasing probability of adverse events as age and volume increases.

Please note that the age and volume categories used in these tables are merely used to help illustrate the increasing rate of adverse events, not to indicate distinct lines of increased risk.

In conclusion, we see that there is still some uncertainty about the best way to assess mid-face volume deficit. Still, the Sponsor has demonstrated statistically significant effectiveness, even under a range of sensitivity analyses. The safety of the procedure may depend on the age of the subject and the volume injected.

Thank you.

DR. MIN: Good morning. My name is Lauren Min, and I am an epidemiologist in the Division of Epidemiology, Office of Surveillance and

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Biometrics. I will be presenting the post-approval study considerations.

Before we talk about post-approval studies, we need to first clarify a few things.

The inclusion of post-approval study questions should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.

The presence of a PAS plan or a commitment does not in any way alter the requirement for premarket approval and a recommendation from the Panel on whether the benefits outweigh the risks.

And, lastly, the premarket data must reach the threshold for providing a reasonable assurance of safety and benefit before the device can be found approvable and any post-approval study should be considered.

There are two general principles for post-approval studies. The main objective of conducting post-approval studies is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.

Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

The specific reasons for conducting post-approval studies are to gather postmarket information, including longer-term performance of the

device, data on how the device performs in the real world, that is, in a broader patient population that is treated by community-based physicians and specialists as opposed to highly selected patients who are treated by investigators in clinical trials; also evaluation of the effectiveness of training programs for use of devices and evaluation of device performance in subgroups of patients, since clinical trials tend to have limited numbers of patients in certain vulnerable subgroups of the general patient population; and, lastly, to monitor adverse events, especially rare adverse events that were not observed in the clinical trials. In addition, post-approval studies can also address any other issues that may be identified by Panel members based on their expertise.

When designing a post-approval study, the following elements must be included: a fundamental study question or hypothesis; safety endpoints and methods of assessment; acute and chronic effectiveness endpoints and methods of assessment; and a specified duration of follow-up.

An increasing number of individuals are receiving dermal fillers. In 2012, an estimated two million people had soft tissue filler augmentation, which represents a 205% increase since the year 2000.

The treatment effect of Juvéderm Voluma XC for mid-face volume deficit is temporary. Therefore, patients may seek repeat treatments. And, furthermore, with patients starting to receive dermal fillers at younger ages, patients may receive multiple treatments over a lifetime. It is not

known if the long-term safety profile of repeat treatments will be different from that of initial treatment.

For the post-approval study, the Sponsor has proposed to conduct a statistical evaluation of data that are being collected in the premarket pivotal study. The study objective is to evaluate the safety of repeat treatment with Juvéderm Voluma XC in subjects with mid-facial volume deficit. The study hypothesis is that the incidence of device- and injection-related adverse events after repeat treatment will not be more than the incidence rate within a 5% margin for device- and injection-related adverse events after the initial and touch-up treatment. This will be evaluated in at least 125 subjects who participated in VOLUMA-002 and also received repeat treatment.

The follow-up duration is 12 months after repeat treatment, and safety endpoints include presence, severity, location, and duration of common treatment site responses and any adverse events after repeat treatment. There are no effectiveness endpoints. And statistical analysis includes summary of common treatment site responses and adverse events and a one-sided 95% unmodified Wald's confidence interval for difference in incidence rate of device-related AEs after initial and repeat treatment.

The PAS proposal was assessed by the FDA review team and found to be generally appropriate and acceptable. Analysis of 12-month follow-up data after repeat treatment is a reasonable postmarket plan that

will provide necessary information on the long-term safety of Juvéderm Voluma XC after repeat treatment. Enrollment for the PAS is complete, as all patients for the study were enrolled during the pivotal premarket study.

Assessment of the presence, severity, location, and duration of common treatment site responses and adverse events are appropriate for evaluating the safety of Juvéderm Voluma XC after repeat treatment, and a proposed statistical plan is acceptable for the longer-term safety evaluation.

The Sponsor has proposed to evaluate the long-term safety of repeat treatment with Juvéderm Voluma XC using 12-month follow-up data from subjects enrolled in the premarket study. The proposed PAS plan addresses the postmarket concern identified by the FDA review team.

However, FDA would like to receive input from the Panel on the following: If FDA determines the premarket data demonstrate product safety and effectiveness, please discuss if there are additional concerns that should be evaluated in the postmarket setting.

This concludes my presentation on the post-approval study considerations.

DR. LoCICERO: I would like to thank the FDA speakers for their presentations.

Does anybody on the Panel have a brief clarifying question for the FDA? And please remember that we will have an opportunity to ask further questions of the FDA during the Panel deliberations later this

afternoon.

Dr. Alam.

DR. ALAM: Thank you.

With regard to the issue of the ischemic optic retinopathy that was seen in one patient, that was eight months after the last injection. I just wanted to clarify my understanding of that. So as far as we know, there was no injection or any other trauma or incident event between the time of the previous injection eight months ago and the development of the retinopathy. And this is a multi-part question.

And then there are also nine other reports of vision abnormalities, and I'm assuming those were something transient that went away.

And then, finally, did the company share with you any similar data about vaso-occlusive issues potentially being associated with ocular abnormalities from their patients treated outside the U.S.?

Thank you.

DR. NIELSEN: Sure. So in response to the first part of your question, that's my understanding as well, that there weren't any events subsequent to that. But I'd like to ask our medical officer. She can explain in more detail.

DR. ALEXANDER: It is correct that she had the event. She noticed the event in one eye approximately eight months after her injection.

She had no other treatments that I'm aware of between there. She was found to have a visual field abnormality in the opposite eye that she had not noted, so we don't know the duration of that.

As far as nine other -- the nine you might be referring to was nine sites of hyaluronidase injection in a different patient.

DR. ALAM: Maybe I'm confused, in which case --

DR. ALEXANDER: I'm not aware of any other visual abnormalities in either this study or internationally.

DR. ALAM: That's very helpful, thank you.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I just wanted to say, apropos, that it was interesting that she had a second injection four months after this visual abnormality.

DR. ALAM: Yeah, here it is. It is on page 35, Table 18, the third line from the bottom, vision abnormalities, nine, 0.0017%. I don't know if you have that.

DR. NIELSEN: We do have that, and I think if you give us a moment, I think we need to consult that table. That's on page 35 of the FDA Executive Summary; is that correct?

DR. ALAM: Yes.

DR. LoCICERO: While you're looking for that, Dr. Miller has a question.

DR. MILLER: Yes, I wonder if you could just clarify for me. On page 28, it's mentioned that there is like, I think, 30% of an adverse reaction. And then, on page 37 it says that there were 78% of patients who had adverse outcomes.

DR. ALEXANDER: I think you're referring to the common treatment responses versus adverse events.

DR. MILLER: I'm not sure. On page 28 it says adverse events, 33% of patients had adverse events. And then, on page 37 it says 78% of subjects had adverse outcomes, they felt, that affected their daily activity. What's the difference between those two categories of things?

DR. ALEXANDER: That can include both early on adverse events and the 78 -- I guess I need the same page as you. Do you have a slide number to go with that?

DR. MILLER: Yeah, it's -- well, I don't see a slide number, but on this it's page 28. Yeah. Okay, that was one right there. It's after. Maybe go one more. Yeah, this one says 38. Is there a difference between adverse event and adverse outcome? I mean, because this --

DR. ALEXANDER: Adverse outcomes can include common treatment responses that were more severe in severity. So an adverse event can be a common treatment response that lasts longer than 30 days and is then classified as an adverse event, or it is an adverse event that occurs during the first 30 days that is not considered a common treatment response.

DR. MILLER: So an unpleasant response may be recorded as an adverse outcome but not an adverse event?

DR. ALEXANDER: But not an adverse event, correct.

DR. MILLER: All right.

DR. NIELSEN: So the table that you're referring to on page 35 in the Executive Summary, so that's a summary of the Sponsor's postmarket experience with it. And so there is a vision abnormality that shows up on this table with nine events. We do not have any additional information on those events. The Sponsor may be able to add detail to that, but we do not.

DR. LoCICERO: For further clarification, we'll have the Sponsor maybe respond this afternoon to that particular question, just to give us clarification.

Yes, Dr. Ballman.

DR. BALLMAN: So I just have a question regarding the agreed-upon endpoint, the MFVDS. Was it felt that there was nothing that was validated that would serve as an endpoint for this trial and that's how come it was agreed with the Sponsor that that would be --

DR. ALEXANDER: Yes, exactly, correct. Mid-face volume has not been assessed before, and there's no accepted validated scale for it, so the Sponsor developed this scale with our participation, in trying to find an adequate clinically usable scale for effectiveness.

DR. BALLMAN: Right, because no other measurement existed.

DR. ALEXANDER: Exactly.

DR. BALLMAN: And, again, your feeling on a one-point change, how was that established as being clinically significant?

DR. ALEXANDER: By use of this scale in the validation training, that investigators could distinguish between the two levels, and by looking at the scale to see if it might be reasonable.

DR. BALLMAN: Okay, thank you.

DR. LoCICERO: Dr. McCauley.

DR. McCAULEY: This validation scale by Zbigniew Lorenc, New York, and it's called the Medicis Midface Volume Scale, it's the four-point scale instead of the five that you have. And they had four evaluators, two board certified dermatologists and two board certified plastic surgeons. So they had four evaluators instead of two. And the intra-observer agreement, which is when one evaluator gets the same set of pictures back in greater than two weeks, they had an agreement of 87%, which I thought was remarkable. And for the inter-observer agreement, it was between 72.5% and 87.5%. So there is another option in terms of the scale.

DR. ALEXANDER: I believe that that scale was developed after this scale and after the onset of the study. So that's good that we have another scale that may be used in the future, but I don't believe that that was available when this study began.

DR. McCAULEY: I don't think so either because it was published

back in, I think, December 2012.

DR. LoCICERO: And I'm addressing the 3D digital imaging data. Was that the entire face, or did that address only mid-face volumes? And that's an attempt to find out in terms of these differences in the change in volume. Was that the entire face or just the area --

DR. ALEXANDER: That's a good question. I believe it was the mid-face areas that were injected, but we may need the Sponsor to clarify that as well.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I just wanted to point out that the cosmetics industry routinely uses silicone masks to measure the volume depths and the length of small wrinkles, particularly periorbital wrinkles, and it seems like that might be a possibility to truly quantify the correction and the duration of correction.

And the other thing that I've been thinking about was this. I mean, I think all of us physicians see submalar and medial cheek indentations, but the malar region is usually not indented. So first of all, I wanted to clarify if Voluma is going to be used for enhancing the malar bone, which is cosmetically attractive, because I don't think I've really seen defects in the higher of the three regions.

And it was interesting, in the data you presented, that the patients evaluated the suborbital, which is an area not being directly treated

by this. And it would be interesting to look at the lasting effect in the separate regions, because the malar, I think, is different than the cheek and the submalar.

And it was interesting that only in that one slide that you showed did the patients evaluate four sites specifically, whereas the investigators didn't, and I think that would be an interesting parameter, to look at the four different sites.

DR. ALEXANDER: Right, the investigators did evaluate the three subsets that were injected.

DR. BURKE: Oh, okay, separately.

DR. ALEXANDER: They did. But they did not -- as you say, the patient questionnaire included a --

DR. BURKE: Suborbital.

DR. ALEXANDER: -- suborbital, and that was not part of the investigator assessment.

DR. LoCICERO: Dr. Alam.

DR. ALAM: Regarding your talking about postmarket surveillance, it appeared to me that there might be -- and I'm not sure it's statistically significant, looking at the tables -- slightly less effectiveness and slightly greater risk of adverse events in non-Caucasian populations, and also HIV patients, who are specifically excluded from treatment, even though they might potentially be candidates once this is approved, potentially.

Do you anticipate having any postmarket surveillance or data pertaining to non-Caucasian populations or HIV populations once and if this is approved?

DR. ALEXANDER: You're right that HIV patients, lipodystrophy patients, were not included. That's really outside the bounds of this study and outside what would be an approved use. So I think that would require a whole different study.

As far as the darker skin types, they had a significant number of darker skin types. And Mr. Van Orden, he addressed this somewhat, but we did not find any significant difference in adverse event outcomes with the darker skin types.

DR. ALAM: And also in terms of effectiveness. So the differences that are seen in the table, they're just nominal differences. They didn't rise to statistical significance. I'm just curious because, obviously, the numbers of those patients would be somewhat lower, and it might just have been a sample size issue, but it's just something for you to consider.

DR. ALEXANDER: Right, statistically they did not reach significance.

DR. ALAM: Thank you.

DR. LoCICERO: Yes.

MS. MATTIVI: Kris Mattivi. I'm the Consumer Representative.

So not having any expertise in this area, maybe this is a better

question for the Panel discussion later on, so you can let me know.

But I'm wondering. There's been discussion about the relationship between adverse events and the volume of product injected. And so I'm curious whether there's also a relationship between the volume of product injected and facial structure or facial area, or is there some measure in that way that would also contribute to the amount of product injected?

DR. LoCICERO: Does the FDA want to address that?

DR. ALEXANDER: I'm not sure exactly how to address your question. If it's felt that they have a more significant volume deficit, the treating investigator would want to use a greater volume.

MS. MATTIVI: And I guess maybe this is my physical therapist background, but just thinking in terms of bony structure and differences in the actual area that would be involved based on a person's bone.

DR. ALEXANDER: And I'm sure there would be some patient preference involved as well. I think that's going to get down to the treating investigator and patient interaction somewhat.

DR. LoCICERO: Dr. Ballman.

DR. BALLMAN: So it was found that there was a correlation significant between age and volume and the incidence of adverse events. I'm just wondering, was it looked at? Is there a relationship between age itself and the volume injected? I mean, are we seeing the same thing, that perhaps older patients need more volume?

DR. NIELSEN: I think Mr. Van Orden is in a better position to answer that. It's my understanding that there wasn't a relationship between the two, but I think --

MR. VAN ORDEN: So there wasn't an interaction as far as breaking adverse events between age and volume.

DR. BALLMAN: No, I'm wondering, was there was a relationship? Did you look at was there a correlation between the volume injected and age?

MR. VAN ORDEN: There might be a small correlation, but they're both significant in the model when they're in there independently. I don't have the numbers for, exactly, the increased volume with age, but I think they independently affect adverse events.

DR. BALLMAN: Perhaps, but if there's co-linearity between the two variables, it might be a little bit harder to interpret.

MR. VAN ORDEN: That's true. But if there was a strict linearity, one would be -- they wouldn't both be significant in the model like that, then, yeah.

DR. LoCICERO: But that specific question was not answered or not asked ahead of time so that we know that, for one, age --

MR. VAN ORDEN: We can work on clarifying exactly what the volumes were.

DR. LoCICERO: -- causes adverse events and volume causes

adverse events. But we don't know. We have age results and higher volume.

MR. VAN ORDEN: I would also say we can get the exact numbers, but the volume injected and the adverse events do depend a lot on the site and the investigator and how they -- and certainly assumed that subject as well. But there are lot of factors going on here, and it is hard to tease some of this out.

DR. LoCICERO: Dr. Miller first.

DR. McCAULEY: Is there a difference between volume injected -- or let me put it this way. Is there a difference in technique with respect to the amount of Juvéderm that's actually injected and age?

DR. LoCICERO: I think that probably will be a question for the Sponsor, and let's ask them this afternoon.

Dr. Miller.

DR. MILLER: The study was designed with different regions that were injected, but there were no data presented or broken apart by the different regions. Was that an oversight, or was it just not found to be necessary to look at volumes and technique in these different areas of the face?

DR. NIELSEN: So are you speaking in terms of effectiveness or safety or both?

DR. MILLER: Well, in the study design, there's that drawing of the three different regions on the face where injections were made, but then

there was no analysis based on those regions. Was there a purpose for that, or was it just something that was found not to be necessary as you went along in the study?

MR. VAN ORDEN: I'll say, the one that -- it's my understanding that investigators -- each subject may not be treated the same in each of the regions. And so it is harder to say that all subjects should see the same benefit in each region. There was also less agreement in the -- there were MFVDS scores given by the evaluators for each region, and there was less agreement between the two evaluators for those subregions. I mean, the trends towards benefit are still the same, but we just prefer not to make any statements about, you know, determinative statements about benefit.

DR. MILLER: I'm just curious about, like, were 90% of the patients injected in this submalar region and 1% injected on the zygomatic arch?

DR. ALEXANDER: No, the Sponsor did -- and they can present, maybe, more specifics. They did carefully record how much volume was injected into each of the three areas on each side. So we've got patient-specific data on what volumes, and most patients had volume equally distributed through all areas. There were some patients who had more deficit in one and didn't receive injections in others. But, by and large, the patients had all regions injected each session.

There is a slide in your packet. The secondary endpoint was the

evaluators' MFVDS score for the three regions, and it supported this. The numbers are in the 75% range, and there is a slide in there that shows that. And I'll find it for you later if you'd like to see it.

DR. LoCICERO: While we're trying to get that, Dr. Burke.

DR. BURKE: Apropos this, I still think that injecting on the zygomatic malar area is enhancing kind of a bone that's there. That's not usually a defect, whereas the submalar and the anterior malar are defects. So I think that they're treating two different kinds of things. I mean, surgeons would put a malar implant over the zygomatic bone, but these are defects. So I think that it's almost you're talking about two kinds of indications for the Voluma.

DR. ALEXANDER: That certainly could be true, and I'd appreciate the Sponsor's response as well. But I think with aging there is some gravity effect and sometimes the cheek pad will descend and patients -- it is age related and some volume at the superior end of that could be useful to correct it.

DR. LoCICERO: Do we have that slide now?

DR. ALAM: May I ask a question while we're waiting?

DR. ALEXANDER: Sure.

DR. LoCICERO: Yes, Dr. Alam.

DR. ALAM: There was some mention, not so much in the presentation but in the written materials, about the intracutaneous reactivity

test that initially apparently was failed and then it was repeated several times and the results were satisfactory. There was also a note on page nine that based on those findings cumulatively, a short-duration irritation response may be expected. Can you expand on that and discuss any concerns, or lack thereof, you may have?

DR. NIELSEN: So the initial study is a 3-day study, the intracutaneous study, and in that study, as we mentioned in the presentation, there was evidence of significant erythema in that study. That study was repeated by the Sponsor with a longer-duration study, and it also included histology as well. So it's a more carefully done study, but it was evaluated in the same irritation response. And in that study there was also an irritation response very early, and then, with the longer time course of the study, we were able to follow the course of that response and see that it declined very quickly, within three or four days, down to a minimal level.

And the other important part of that study design was that it included -- this time it included approved controls, the Juvéderm approved products as controls, and those controls performed very similar to the product. So with those data in hand, we felt comfortable with the response.

DR. ALEXANDER: Here we go. The Month 6 responder rate for each individual area, for the zygomaticomalar region, was 75.5%, the anteromedial cheek region was 83% and the submalar was 77%.

DR. LoCICERO: Dr. Miller wants to follow up.

DR. MILLER: Thank you, I didn't see that before, but I do have another question for you. I know we're going to discuss this afternoon the photographic assessment, probably. But across the different areas it was, maybe, talking about how this was done standardized, I mean where there's standardized lighting and distance from the camera to the subject.

And on the 3D assessment with the 3D photographs, what was the methodology used to determine the volume on that?

DR. ALEXANDER: I'm sure the Sponsor can specifically answer that. The Canfield Vectra system was used, and they took photographs from two angles and did volumetric calculations. So it was a calculated volume.

DR. LoCICERO: In terms of housekeeping for the FDA, for our printed form of your slides, blue on mauve does not work, and you might consider another color palette.

Do we have any -- yeah.

MS. MATTIVI: One more question. The other thing that I'm curious about are, although there were not many, the three events that were late-developing adverse events and what might have been coming into play with those late-developing events. I can understand the ones that continued on from initial treatment, but I'm just curious about the late-developing ones.

DR. ALEXANDER: Well, that's why we raised the issue. It's a very small number of patients, but it's something to consider. The etiology is not known, but it can be granulomatous changes, it could be infectious

changes, which it did not appear to be in this case. So that's the question we'd like to discuss.

DR. LoCICERO: We will expand on that this afternoon.

Are there any additional questions for the FDA at this time?

(No response.)

DR. LoCICERO: Thank you. We are surprisingly running slightly early, but we will now break for lunch.

Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in approximately one hour at 12:45. The room will be secured by FDA staff during the lunch break. You will not be able allowed back in the room until we reconvene.

Thank you.

(Whereupon, at 11:40 a.m. a lunch recess was taken.)

AFTERNOON SESSION

(12:51 p.m.)

DR. LoCICERO: It is now 12:51, and I would like to resume this Panel meeting. We will now proceed with the Open Public Hearing Portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: 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 any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of 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 have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your

statement, it will not preclude you from speaking.

DR. LoCICERO: We received multiple requests to speak. We ask that each of you speak clearly into the microphone to allow the transcriptionist to provide an accurate record of this meeting. Each speaker will get four minutes to speak, and we're ready for the first speaker.

Is Dr. Diana Zuckerman here?

MS. KENNEDY: Good afternoon. My name is Caitlin Kennedy, and I am a senior fellow at the National Research Center for Women and Families. I am reading the statement of our president, Dr. Diana Zuckerman, who could not be here today.

Our nonprofit research center does not accept funding from pharmaceutical or device companies, so I have no conflicts of interest. We scrutinize research to determine which medical treatments are safe and effective for adults and children.

The benefits of a dermal filler are cosmetic and can also affect quality of life, so any cosmetic or health risks must be weighed carefully before the FDA makes a decision about approval.

The effectiveness scale of the Mid-Face Volume Deficit Scale hasn't been used before to support FDA approval, and it isn't scientifically reliable. Inter-rater and between-site reliability was very low. FDA scientists point out that there was exact agreement for the two live evaluating reviewers only 41% of the time. The two evaluators often differed by two

points or more on a six-point scale, sometimes differing by four points.

The objectivity of these reviewers is questionable since the patients were less likely to report an improvement of one point or more than the reviewers were. The MFVDS scores at post-six month time points showed even lower levels of agreement.

Patient satisfaction scores are high, but these are not considered scientifically valid because of cognitive dissonance and because many patients don't want to take the chance of offending the doctor that they depend on when things go wrong.

Given these questionable benefits, what are the risks? This Juvéderm Voluma product has many short-term complications, such as pain and swelling, as do similar products. Of greatest concern is that 78% were moderate or severe, as FDA scientists pointed out. Most had moderate complications which are of sufficient severity to make the subject uncomfortable and influence daily activities; 19% had severe complications that caused severe discomfort and compromised performance of daily activities.

After 30 days, these complications are called adverse events. Fifty-two percent had adverse events, although the doctors did not always report that they were related to Voluma. But even 20% is too high to ignore. That did not include complications or adverse reactions after the second treatment, or patients who dropped out of the study for reasons that were

not reported but could have included adverse events.

If a person is choosing this product to look and be their best, especially for a special occasion, it defeats the purpose if there is a substantial risk that they might look worse rather than better.

We are also concerned that there were so many exclusion criteria for the study and that the average age was only 54. This doesn't give enough information about safety or effectiveness in the real world, especially for older patients.

In the ideal world, patients would be told exactly what the likely benefits and risks are as part of informed consent and could decide whether to take the chance. However, in the real world, we know that many consumers are not being given accurate, understandable information to make an informed choice. Even if provided in writing, most consumers will rely on the physician's recommendations, not written warnings.

Please urge the FDA to use a higher standard of safety and effectiveness before approving this product, including research on older patients and larger volume. This product is not urgently needed, so a postmarket study is not good enough. If a cosmetic dermal filler leaves many patients looking and feeling worse instead of better, it is not effective.

Thank you.

DR. LoCICERO: Thank you.

Dr. Glaser.

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DR. GLASER: Good afternoon. I'm Dee Anna Glaser. I'm a board certified dermatologist. I'm a professor and the Vice Chairman of the Department of Dermatology and the Chief of Cosmetic and Laser Surgery at St. Louis University School of Medicine. I'd like to thank the Panel for granting me the time to share my perspectives with you today.

As a disclosure, I do want to tell you that the Sponsor provided me with travel assistance to be here today. I have served as an advisor for Allergan in the past, and my institution did receive monies for my participation in the Allergan-funded trials.

I'd like to tell the Panel that I fully support the approval of Juvéderm Voluma XC for the treatment of mid-face volume deficits. I base this on my more than 20 years experience using injectable fillers and as my experience as the PI and the injecting investigator for the VOLUMA-002 trial. In the trial, I had the two roll-in subjects as well as 25 subjects that I treated.

In terms of the filler, I found the product to inject very smoothly, and it had very nice flow characteristics. I felt like I could deliver exactly the amount that I needed to, in the exact and precise spot that I wanted the filler to be at. I found the results in the mid-face to be very soft, very natural, and beautiful. It had excellent durability in my subjects, lasting 20 to 24 months. Subjects seemed to be very satisfied with their treatments, and they liked the look and the feel of the filler.

The safety profile was good, in my opinion, and the related AEs

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that I saw were what I had anticipated based on my experience with other hyaluronic acid fillers. Bruising and post-injection tenderness is common, and especially when injecting higher volumes at that deeper layer, as we did in the study. Some of my patients noted firmness and lumpiness. But on my evaluations, it was just what the expected filler would be like for that type of volume procedure that I had done.

I'd like to say to the Panel that I really feel that this product will fill an unmet need. The use of fillers has dramatically changed over the past 20 years, from the days when I used bovine collagen just to fill lines to what I do now, which is volume replacement for many of my patients. There is currently no FDA-approved HA filler for use in the mid-face. And now approximately 50% of my filler patient procedures are getting mid-face volume injections. I perform over 1,000 procedures with fillers each year, and the trend is only increasing as to the number of patients that I inject in the mid-face.

It's very important to me and to my patients to have an FDA-approved filler that is well studied and well suited for mid-face volumizing, and I think that this filler should be a hyaluronic acid.

I found Juvéderm Voluma XC to have excellent injection characteristics, a good safety profile with AEs, that I find typical for this kind of procedure and the volumes that I used. The results were soft, beautiful, and natural, and there was good durability.

Again, I'd like to thank the Panel for allowing me to share my experience with you. And, again, I'd like to repeat that I am in full approval of this filler.

Thank you.

DR. LoCICERO: Thank you.

Dr. Green.

DR. GREEN: Us dermatologists are very visual, so I figured I'd show some slides.

Okay, welcome and thank you, members of the Committee, for letting me speak. My name is Lawrence Green. I'm a dermatologist who practices locally in the area. I'm on staff at George Washington Hospital.

As far as disclosures go, I do clinical trials in my office quite frequently. It's a part of my practice. I have done clinical trials for Allergan related to acne and an eyelash enhancement product. I have never done a clinical trial for Allergan on one of their wrinkle fillers, although I have done clinical trials with other companies' wrinkle fillers, but not Allergan.

I'm here today representing the American Society for Dermatologic Surgery Association. I'm representing over 5700 dermatologists throughout the United States, and this group of dermatologists is uniquely involved in procedural dermatology. That's our expertise, which wrinkle fillers are a part of. The ASDSA is also a publisher of the scientific journal *Dermatologic Surgery*, which is very well read and respected.

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So I'm here to talk about Voluma. As you have heard throughout the morning and from other speakers, it is a newer hyaluronic acid, but it is a hyaluronic acid. It's different than others in that it adds low molecular weight HA to add more volumizing and contouring. It's a routine structure without migration from deep injection sites, as you know.

But I think the most important thing, at least from a dermatologist standpoint, and I think I'm speaking for all of our members, is that it is reversible. Other deeper volumizing fillers that currently have approval are not reversible, and this is the first one that's seeking approval that is reversible with hyaluronidase. And to us, as a doctor, from a safety standpoint, this is very important.

So, in summary, our members are the most users of hyaluronic acid fillers in the United States, we represent. The ASDSA is very supportive, including myself, of FDA clearance for Juvéderm Voluma.

As Dr. Glaser mentioned, this is an unmet need. We do not have any FDA-approved fillers to treat the mid-face. Whether it be submalar or anteromedial cheek, we have nothing FDA approved. And I can speak for myself and, I'm sure, other dermatologists around the country, members of our society, that we are asked every day from our patients for something to treat the mid-face, and we don't have anything FDA approved.

So this is a big advance, from our standpoint, for something to seek, a wrinkle filler to seek FDA approval. And most importantly, it's an

advance that is reversible in terms of if any side effects have occurred that the patient does not like.

So the ASDSA supports the data in the clinical trial as accurate and well done. Our leadership has reviewed the clinical data, including the president and president-elect as well as many board members, and it is our opinion that the benefits of Voluma well outweigh the risks.

Here are some references that were written by our membership and our leadership that discuss Voluma that I'm sure you're aware of but are for your reference as well.

Thank you.

DR. LoCICERO: Thank you.

Dr. Graivier.

DR. GRAIVIER: I want to thank the Panel for allowing me to come today. I'm Dr. Miles Graivier, a board certified plastic surgeon from Roswell, Georgia, just a suburb of Atlanta.

Disclosures: Today I'm representing the American Society of Aesthetic Plastic Surgeons, and I'm a spokesperson for the American Society of Plastic Surgeons. I have no financial or future relationship with Allergan Medical. I've not done any of their clinical trials.

Just to review very briefly what the statistics show in the recently published American Society of Plastic Surgeons and ASAPS filler statistics, it shows that there were more than two million soft tissue fillers

injected in 2012, which represents an increase of 5% from 2011. So it's a large number. And as you see, the percentage of hyaluronic acids that are injected dominate the market, with 71% of these injections being HAs.

In my personal experience I've injected, just like Dr. Glaser and most people that are here today, more than 10,000 patients with fillers. I've authored more than 20 scientific papers published in peer review journals and textbooks, including several review articles and recommendations regarding fillers. I've been a panelist and presenter at numerous national and international meetings, and a Phase III trial participant in numerous fillers, although none for Allergan.

As Dr. Glaser mentioned, the way that we utilize fillers, and I utilize in my practice, started with line filling, but we graduated to volume filling and kind of a structured volumetry. So there is a need for more of a structural filler that has more viscosity, more lift, and less displacement when force is applied to it. We find that the old term of line filler is somewhat old. We need to actually provide volume and structural support as well.

As just mentioned by Dr. Green, there is a need for these higher-viscosity, higher-resistance fillers, and the current best choice that we have that are FDA approved at present are calcium hydroxylapatite and polylactic acid. We do need a filler that provides more structural support that has a hyaluronic acid base. Why? Because they're the most commonly used product, as we've seen. Also, as Dr. Green showed, they are the most

reversible. They're the only product that has a reversible agent, hyaluronidase, that the majority of people are comfortable with, a majority of injectors are comfortable with, as seen by statistics in 2012.

Even when late granulomatous effects, which are not noted in the trial because they occur at very late times, usually after a year, if these occur with hyaluronic acids, they're less severe. They're more self-limiting than in other non-hyaluronic acid products. I therefore find a need to have a volumizing mid-face filler that's a hyaluronic-based filler such as Voluma.

Thank you.

DR. LoCICERO: Thank you.

Dr. Butterwick.

DR. BUTTERWICK: Good afternoon. Thank you for this opportunity to speak. My name is Dr. Kimberley Butterwick, and I am a cosmetic dermatologist practicing in San Diego, California for the past 23 years.

My disclosures include that I'm one of the principal investigators for the Juvéderm Voluma clinical trial, and I'm on the advisory board for three filler companies, including Allergan. Allergan has paid for my travel expenses here, but I've received no reimbursement for the time out of the office.

I've been volumizing with facial fat since the 1990s and use synthetic fillers daily, like the others here. To date, I've injected over 200

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syringes of Juvéderm Voluma, and I truly believe in this product for four reasons: location, efficacy, safety, and duration. First let's take location.

Voluma is the only filler to be studied for mid-cheek enhancement, and this is a very important area in an aging face. From recent studies, we know that there are over six fat compartments just in the mid-face alone, and they atrophy with age. There are also changes in the maxillary bone underlying these compartments, recession and rotation, such that the soft tissue above it sort of falls off the ledge. Consequently, the skin sags, creating the nasolabial fold and drooping into the jowl. It's really not gravity; it's volume loss in the cheek that makes us look old. Replacing the volume here gives more natural results than just filling the nasolabial fold, because it addresses the cause of aging. So I think this area is very, very important.

Second, because of the structure, you've heard, Voluma has an amazing ability to lift and restore contour more effectively than any other synthetic filler I've used. Other fillers would require many more syringes to get the same effect and therefore be more cost prohibitive. It's also softer after initial swelling resolves than many of the other fillers I've used. Voluma's efficacy is actually similar to autologous fat, giving that same beautiful contour for the cheek but without the surgical procedure, the sedation, the risk of infection, and irregularities not only in the recipient site but the donor site as well.

Third is safety. Voluma is very safe, and it has a side effect profile very comparable to other HA fillers, in my experience. Nearly all subjects at our site reported only mild minor to moderate bruising, swelling, firmness, lumpiness of short duration.

One subject that you have noted here was my patient, and she had 10 cc injected in her first session, and she reported severe firmness up to 69 days. However, upon reading her diary, it was severe only in the first 24 hours and then subsided to mild to moderate for 20 days. After day 20 and until 69, she only reported mild firmness, which by definition was barely noticeable. This was not visible, it looked smooth, the patient loved the product, had a retouch-up at one month with 1.2 cc, and at two years she only needed one syringe to maintain her correction.

Enhancing Voluma safety, as you've heard, is the ability to dissolve this product with hyaluronidase should any problem or inadvertent placement arise.

Lastly is the duration. I've been struck by this duration, you know, excellent correction at one year and up to two years. That overshadows what we have now.

Thank you for allowing me to share my experience with this product. I strongly recommend it be made available to the public.

DR. LoCICERO: Thank you.

Nathaniel Wilkins.

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MR. WILKINS: Good afternoon. My name is Nathaniel Wilkins. I'm 59 years old. I own Nate's Total Body of Health, Wellness, and Fitness Company based in Miami Beach, Florida. My company provides fitness services and consulting to five-star resorts, hotels, and condominiums. I'd like to thank the FDA for giving me the time to speak today.

While Allergan is reimbursing me for my travel and lodging, I'm pleased to take the time from my schedule to attend this meeting and share my personal experiences with Allergan Juvéderm Voluma XC.

As a seasoned fitness professional, I can tell you that presentation in terms of appearance is a critical factor in gaining new business and clients. I knew that my face was beginning to appear a bit drawn and the volume was decreasing because of age. Initially I was apprehensive about participating in the study because I'm a little bit squeamish, but encouragement from a friend, who had great results with fillers, allowed me to participate. As it turns out, after months of participating in the study, I had the same great results.

I'm better for my experience with Juvéderm. I tell you that although I'm a man, again, I was squeamish about injections, but this wasn't painful at all. And the best part about it was that there were instant results. Within minutes I looked more youthful and perhaps 10 years younger. I believe the product actually benefits or has benefited me professionally. The upside potential is what motivated me to participate in the trial, and it was

only the upside potential that I received.

I hope this product will be made available to the public because I'll recommend it to my friends and family, and I'll do it again for myself.

Thank you so very much.

DR. LoCICERO: Thank you.

Lisa Epstein.

MS. EPSTEIN: Hello. Good afternoon. Thank you to the members of this FDA Advisory Committee for accepting my request to speak and present my views on Juvéderm Voluma XC. I strongly support its approval.

In my experience, it was very safe, well tolerated, and replaced lost face volume with great filling power and a natural, bouncy, long-lasting, beautiful result.

My name is Lisa Epstein, and the Sponsor has covered my travel and lodging expenses to attend this meeting. I am a registered nurse, and over the course of my nursing career, I've worked at the National Institutes of Health and later specialized in oncology. Both experiences led me to deeply appreciate the importance of clinical research volunteers and to advance the body of medical knowledge.

In the fall of 2009, I participated in the U.S. Voluma trial. Over the course of the trial, I received three treatments with Voluma. I was randomized into the immediate treatment group, and on November 23rd,

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2009, the study dermatologist injected several syringes of Voluma into both of my cheeks. I returned one month after my initial injections, and due to some minor unevenness, one additional syringe was injected into my left cheek.

Then, two years and four months later, at the completion of the study, I received a final injection of two syringes in late February 2002 [sic]. But I believe, at that time my facial improvement, dating back to my original treatment in the fall of 2009, still persisted and I did not need to be injected with as many syringes as I had originally received.

In my opinion, the original treatment was not completely absorbed until October 2012, which was a full three years after my first treatment with Voluma. I never noticed any product migration, and throughout the study period and beyond, I was extremely pleased with the good, long-lasting aesthetic result. The aesthetic result was immediate, subtle, and provided resilient bounce and increased density to my cheeks.

The side effects I experienced never interfered with my active and busy working mom lifestyle. They were more noticeable with the first treatment, when I had received a greater amount of the product. I had declined the pretreatment lidocaine. The injections themselves only caused slight discomfort. In the immediate two to three days post-initial treatment, I did experience some slight swelling and redness and noticeable bilateral soreness and tenderness, which was easily managed with applications of ice.

I remember that I could feel lumped product in my cheeks for about two to three weeks, after which the Voluta was distributed smoothly and evenly in the treated areas of my cheeks. And that was only after the first treatment, when I received more syringes full than other treatments. I had very slight bruising in one of the injection sites. These side effects were not noticeable with the second and third treatments, when I received much less of the product. At no time did I miss work, social, or community volunteer activities that are part of my daily life.

I am grateful to the Committee for this opportunity to present my unique perspective on Voluta as a participant in the U.S. study. Again, I strongly support the FDA's approval of this product. And thank you for your time and your interest.

DR. LoCICERO: Thank you.

Barbara Herrera.

MS. HERRERA: Good afternoon. My name is Barbara Herrera. I'm an emergency room nurse. I'm also a mother and a grandmother. I would like to thank the FDA for allowing me to share my experiences with the Voluta trial study.

I'd like to begin by saying that overall wellness includes looking and feeling your very best. About three years ago I started to look into facial plastic surgery to improve my overall look, when I was informed of the Voluta research. I was a little nervous at first and then I felt better when the

staff took their time to explain all the details.

I had 3D photos taken before and after each visit to see how the treatment was working. The procedure was over in a few minutes. I experienced no pain, only mild swelling and bruising, which disappeared in a few days. I knew right away that my appearance was amazing, that I looked so much younger. Kudos to Dr. Baumann from the Research Institute that helped me look my best.

This was a total transformation for me. For once, I couldn't wait to go to work so everyone could see my facial improvement. All of my coworkers were asking me what I did because I looked so much younger. Most of the patients I take care of, they're always giving me compliments and think that I look younger than I am. It's important for me to feel good and to look good, which helps me feel more confident and happy.

I also enjoy taking pictures now with my new look. Strangers even think I'm the mother of my grandchildren. I am extremely satisfied with the results. It has totally uplifted my spirits. Voluma has given me a positive outcome with long-lasting effects. The Voluma injections have lasted over two years for me, and I still get full compliments. I had my first injection in April 2010 and my second injection in June of 2012. I still look and feel great.

I have been truly lucky to be spared a costly facial cosmetic surgery that would have more increased risk of side effects and require time away from work to heal. Voluma has fewer side effects and requires no time

from work just to achieve the same beauty results.

As I said earlier, overall wellness includes looking and feeling your very best. I am so grateful for the Voluma Sponsor that made it possible for me to be here. Thank you, Voluma, for making me look younger again.

Thank you.

DR. LoCICERO: Thank you.

Linda Bates.

MS. BATES: Good afternoon. My name is Linda Bates. I'm a mother, a volunteer, a world traveler, and a lawyer. Physical and emotional wellness, as well as an age-appropriate youthful appearance, are important to me. I'd like to thank the FDA for allowing me to speak about my experience as a participant in the Voluma trial. It was a positive experience that delivered long-lasting natural results.

I've always been generally pleased with my appearance. Nonetheless, I've battled under-eye puffiness since my late teens. As I matured and began losing mid-face volume, the puffiness became more pronounced. I researched my available options and was in my doctor's office preparing to undergo my initial treatment with another product when the doctor informed me about the Voluma trial. I decided to participate in the trial, not to change my appearance but rather to maintain it. That's exactly what I got with Voluma.

My cheeks were filled in a subtle, natural way. I look like

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myself. Moreover, although the results had reversed somewhat, the effects were still clearly visible at the two-year period, at the two-year retreatment period. The added confidence of looking good felt great and reflected positively in every area of my life. I was retreated after two years, and I'm still reaping the benefits of the Voluma treatment.

In summary, my experience was positive. I experienced very little discomfort, a slight bruise under my left eye after the initial treatment, and no bruising at the retreatment. A week after treatment, my face felt soft and natural. I did not experience any downtime following either procedure. My results were exactly what I wanted and lasted two years.

Based on my experience, I strongly support marketing Voluma in the United States. It's my hope that the FDA will grant its approval so that I and others like me may benefit from the product in the future. Thank you for your consideration.

I have no financial relationship with any party here, and the Voluma Sponsor reimbursed my travel and lodging expenses.

Thank you.

DR. LoCICERO: Thank you.

Rose Hodges.

(No response.)

DR. LoCICERO: Deena Libman.

(No response.)

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DR. LoCICERO: Barbara Escarra.

MS. ESCARRA: Good afternoon, everyone. My name is Barbara Escarra. And, first of all, I would like to thank the Food and Drug Administration for allowing me to speak in this Open Public Hearing to share my experience with Voluma.

I'm in my early fifties, and as I started aging and observing my physical appearance change, I wished I could just stop the clock and revisit those years when everything was in place, including the volume of my face.

I work in the sports industry for the Miami Dolphins and the Miami Heat. So as you can imagine, I am constantly surrounded by young and pretty faces, and I'm not talking about the players.

I was fortunate to be referred to Dr. Baumann's study through a friend. I was skeptical at first, especially since I'm not a needle-friendly person. But after doing some research, I found out that Dr. Baumann was a well-known dermatologist with years of experience and also was well established in the research community, so I decided to give it a try. The staff was amazing. They thoroughly explained the study to me and allowed me to ask any questions I might have had. After various tests and pictures, I was accepted as a candidate for the study, and the journey began.

The injections were totally painless, and there was no downtime. I believe you could actually get this procedure done at lunchtime and go back to work. I felt no discomfort during or after the procedure, and

best of all, I was 100% satisfied with the results.

And I'm here to say, the filler has provided a life for me, not only externally but internally as well. I no longer dread taking pictures. My self-esteem rocketed. I began to be more sociable and even sexy, if I might dare say. I have nothing but great things to say about Voluma.

I hope that after hearing the enthusiasm from me and the rest of the individuals who have participated in the study, the Food and Drug Administration would approve this cutting-edge remedy to aging.

I also want to thank Allergan for reimbursing my travel-related expenses so I could be here to share my experiences with you.

Again, thank you so very much.

DR. LoCICERO: Thank you.

Matt Marfoggia.

MR. MARFOGLIA: Good afternoon. My name is Matt Marfoggia, and I'm from Los Angeles. I'm quite happy to be here to speak with you today about my experience with Voluma.

First off, I'm someone who's always had a fairly fast metabolism and, as well, a rather leaner-type build, in addition to always having had a fairly active lifestyle too. I've been a waiter for quite a long time in very fast, high-volume places, keeping me on my feet and thus adding to my already fast metabolism.

A few years back, right after I turned 40, I had to increase my

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work hours as well as adding a new fitness regimen. I got into great shape and thus leaned out even more. At that point, however, I could see that I had lost what appeared to be a significant amount of volume in my face. It happened really fast, or so it felt, and it just seemed that there was this youthful robustness missing. The whole thing was a strange irony for me because here I was healthy and in great shape, but the loss of volume in my face ended up making me depressed and causing me a great loss of self-esteem.

The other aspect of this whole experience that was extremely disheartening, especially as a healthy 40-year-old man, was that there was very little out there research-wise for me to find out about this issue. I felt somewhat alone and definitely the odd man out with this situation.

It was then, a few months later at an annual checkup for a skin check with my long-time, long-trusted dermatologist that I expressed the concern I had regarding my loss of facial volume. He told me that what I was experiencing was not unusual. In fact, it was more common than I was aware of. He also told me then of the Voluma trial.

Without hesitation, I truly believed I had nothing to lose, so I began the trial at the end of 2009. Not only did I have no negative side effects whatsoever, but my positive effects from the treatment were immediately exactly what I had hoped for. From others, it would be as simple as Matt, you look great, as opposed to did you do something, which was

exactly what I had wanted because I didn't want it to look like I had really done something. And for me, when I looked at myself in the mirror, it just brought back that youthful robustness and volume I felt I had lost, which in turn brought me renewed confidence.

After about 18 months, which was July 2011, I was retreated with the product, and I can honestly say that even while that was close to two years ago, my facial volume has never gone back down to what it was before I had my first initial treatment with Voluma, which was in 2009.

It is because of my positive experience with Voluma that I hope it is approved as quickly as possible, because I certainly know it's a product that's helped me greatly and want to use again.

While the Sponsor did in fact cover all of my travel-related expenses and lodging, it was of my own volition to come here and tell my story. And I'd definitely like to thank FDA for granting me the time to speak and share my experience with Voluma. The results were exactly what I wanted, natural and long lasting.

Thank you for your time.

DR. LoCICERO: Thank you.

Patricia Garcia.

MS. GARCIA: Good afternoon. My name is Patricia Garcia, and I'm here to let you know that I support the approval of Voluma, and I'd like to share my experience with you. I extend my thanks to the Committee for

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allowing me to speak this afternoon.

I'm here today strictly as a volunteer speaker, and the Sponsor reimbursed my expenses and lodging.

I'm involved in sales, and I'm in constant contact with clients face to face. Presentation and appearance is very important in my line of business. I'm 56 years old, I'm a black Hispanic woman, and I appreciate how Allergan includes minorities in the study.

In February 2010, I participated in the study at a cosmetic and research center in Miami Beach. It was entirely voluntary, and I was one of the lucky ones that was injected with the Juvéderm Voluma gel. I felt that my cheeks needed augmentation to correct age-related volume deficit on my face. I was injected above the corners of my mouth and around the sides of my nose and upper cheeks.

They first administered a numbing agent, and then I was injected with the gel. I had a little discomfort. I was lucky that I had fairly minor swelling and tenderness. I returned one month for observation and follow-up visits every three months for a one-and-a-half-year period. It had long-lasting results for up to two and a half years.

I filled out a log after every month, and they asked specific questions of any noticeable changes in my facial appearance. There were "before" and "after" digital 3D panoramic photographs taken, and they captured the changes in my face, and I was able to see them as well. What I

loved best about the procedure was that I received compliments on my appearance, and no one was able to pinpoint exactly why my appearance improved. And I didn't tell them.

The study impacted me in the way that I do business, and it impacted me positively. There were no negative effects. The staff at the center were wonderful, very caring, informative. They made me feel very special with my participation in the study. And I hope you approve this product because, frankly, I would love to be treated again with Voluma.

Thank you.

DR. LoCICERO: Thank you.

I now pronounce the Open Public Hearing to be officially closed. We will proceed with today's agenda.

Before we completely excuse our public speakers, does anyone on the Panel have questions for any of the speakers this afternoon?

(No response.)

DR. LoCICERO: Thank you very much.

We will now begin the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Is the Sponsor prepared to respond to some of the Panel

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questions from this morning?

DR. AVELAR: If I can, I know that I was to address the ocular, the nine cases, and I think there was also a request for clarification on that optic neuropathy.

Okay. So on the postmarketing, there were nine items there for postmarketing. There was some redundancy, so the nine actually reflected five cases. Two of the cases were -- and these, of course, are in places where they're approved -- were not ocular phenomena, but they were more foreign body in nature. They were used on label, the areas in the cheek area. The patient complained of some dryness or some foreign body sensations, and they all resolved without any treatment or intervention.

The other three. Specifically, one took place in Switzerland, and we don't have all the details, but it was a patient with Grave's disease and very enhanced exophthalmos, and the injection was put in around the side of the eye somewhere, and we were not able to get explicit details. It exacerbated the exophthalmos, and the patient required a decompression procedure. And that resolved, as far as we know.

The other two cases took place in Korea, and they were visual problems that happened acutely during the time of the injection. Both cases were in vascular ridge areas. One was on the glabella, off label, and the other one was in the nose area, and the events took place right around the time of the injection. They went into visual loss.

The case of the optic neuropathy. So that's postmarket in the clinical trial. One of the serious adverse events that we described was an optic neuropathy, and the details are as such. The diagnosis of that event was of an optic nerve stroke, and the clinicians who saw this patient said this was not related to the device.

If we look at the history of event, the patient was injected on June 3rd. It was her last injection, and she was asymptomatic, and on January 27th very specifically woke up with a hemifield vision loss, which is consistent with an optic nerve stroke. It's usually half visual field. She went on to see an ophthalmologist, and she was worked up. She had some things that predisposed it to her. She had migraines, and she was found to have high LDLs in cholesterol.

She was then referred on to another ophthalmologist, and as they followed the patient through, they could see the optic edema decreasing, which again is consistent with an event that took place around January 27th.

The reason why the contralateral eye blindness -- or not blindness, but contralateral phenomena are also relevant was because it was an optic nerve stroke. Quite often the other side is infected also, so it was subclinical to her. But when they actually assessed her contralateral visual field, they found out there was a visual field defect there also that she was not aware of.

And then there was one more case of an optic call, if you will, within the trial. It was a case of iritis, and it took place three weeks after the injection. It was noted as mild, and it was a case of miscoding. So when the investigator was asked about when we inquired, because we obviously were worried and tried to investigate it, she said that was a mistake. It should not have been device related. It was three weeks from the injection.

Those are the cases of the optic.

With regards to the other question, I believe, that was asked was for volume injected into the various regions. And if it's up, we do have that slide and if I can -- volume injected into the regions, which should be D-250. And if we can put up the slide, this gives a sense of the volume that was initially injected into the three major regions of the face. We did track the various regions of the face.

I'd like to ask Dr. Todd Gross up. We were asked a few other questions, and I'll just hand it over to him.

DR. GROSS: I'm sorry, keep the slide up for a moment. There was a question about injections at Month 6, and I just wanted to clarify.

The patients randomized in the treatment group were injected at initial treatment. One month later they returned for a touch-up treatment. Month 6, only control subjects were injected after the Month 6 visit, and they also went through the initial treatment and the touch-up treatment sequence. So I do want to clarify that.

So there were two questions. One was the way that the 3D photography was done. So the 3D photography was done using a Canfield Scientific Vectra imaging system, and this is a picture of the system. It uses two high-resolution cameras at a fixed angle. The system is calibrated using a calibration board every day that it's used, and then the patient is positioned within the system. The lighting is standardized, the resolution of the cameras are standardized, and because of the calibration, it then creates consistent images that are three-dimensional in nature. These three-dimensional images were used during the study.

For example, the evaluating investigators would look at the three-dimensional image as part of their GAIS assessment. They look at the baseline photo and compare it to the live subject. The treating investigator, once the images were taken, would identify landmarks, for example, the corners of the eyes and specific areas at the corners of the mouth. Those landmarks could then be used to overlay two images of the subject, one at baseline and one at follow-up, and calculate a change in volume based on the three-dimensional rendering of the face. So it's a very standardized system.

Somebody asked about correlation between age and injected volume. So we did look at the correlation between age and injected volume. But I also wanted to show -- we included one other variable here, which is the baseline MFVDS, which is reflective of their baseline deficit. And what we found actually -- and I'll take you to the bottom of the slide first. The

correlation between age and volume injected was .19. This is certainly at the weaker end of the correlation range.

But we saw stronger correlations when we looked at age versus baseline MFVDS, a correlation of .26, and between baseline MFVDS and volume injected, a correlation of .35. And what this tells us is that age is not the sole determinant of injected volume. And, in fact, age does drive deficit. But within a specific age group, there can be a wide range of deficit, younger patients with greater deficit, older patients with less deficit, and deficit is one of the key drivers of the volume injected; not the perfect sole determinant of volume injected, but certainly one of the drivers of it.

As a result of these correlations, when we entered age and baseline MFVDS and volume injected into the multiple logistic regression analysis, along with other variables, we did see both a contribution of age and a contribution of volume injected.

DR. AVELAR: And the last question that we had taken note of was -- the question was, was there a difference in techniques that one would use in someone with more advanced age?

DR. JONES: The answer to the question about are there differences in injection technique with age, the basic answer is no; the injection techniques at my site and across all sites were quite varied. It did not correlate with age and ultimately were entirely up to the preference of the injecting physician.

DR. BURKE: I think they answered my questions this morning.

DR. LoCICERO: Dr. Alam.

DR. BURKE: Oh, there's one other thing I just wanted to ask. In looking at the long-term follow-up, if you monitored the weight of patients, because in some of the photos, if you look at the chin, it looks like the patient gained weight and therefore the long-term follow-up would be better. And I just wondered if you looked at that as a parameter.

DR. AVELAR: No, we didn't. That's an excellent point. We did not in this trial.

DR. LoCICERO: Dr. Alam.

DR. ALAM: Thank you for your explanation regarding the optic nerve issue.

On a related note, did you note any instances of vaso-occlusion that might be associated with the time of injection? Specifically, were there any clinical findings of unilateral, focal extreme pain or erythema which might be suggestive of that, or a so-called reticulated erythema that might be suggestive of intravascular occlusion during the injection process or immediately thereafter?

DR. AVELAR: We did not, not in this trial.

DR. ALAM: Thank you.

DR. LoCICERO: Dr. Miller.

DR. MILLER: I'd like to follow up on that question because this

is a complication that we haven't really discussed very much, and it doesn't happen very often, but when it happens, it's actually devastating. And this is with other hyaluronic acid fillers. There have been cases where there have been local necrosis from thrombosis of some of the end arteries in the face as crinnicle bella (ph.) on the lip and on the nose from incidental injection. I believe the thought is primarily it's polymerization inside the artery.

This is different material you're injecting in a different place than these areas. But this is something, I think, that needs to be noted as a possibility for any of these hyaluronic acid-injectable materials. You haven't seen any, but I think if we do and you've done 500,000 patients, which it's pretty amazing it hasn't occurred yet, but what would your comment be about that?

DR. AVELAR: We agree. We agree completely. We realize there is no polymerization effect that happens. The product is fully polymerized. But what happens is, from a retrograde, it can be introduced through the vasculature. To your point.

So we also are aware of the structures that are critical of the facial, the angular arteries, and we have to be very respectful of these. One of the big things that we emphasize is, in the area that we inject, we have these landmarks, and I think all injectors need to be leery of the landmarks and respectful of the landmarks.

In the DFU, we also try to emphasize that. And right now

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where we have it is in one of the warnings that this product is not to be injected intravascularly. Of course, we would take any recommendations from the Panel to make it more robust or accommodate anything that would help emphasize this point.

DR. MILLER: As we proceed with the discussion, I think I wasn't aware of this complication until I saw it, and then, as I looked into it a little bit, I became more aware. This has happened sporadically, and I think that it needs to be -- I think, typically, many practitioners are not aware of it until they personally experience it. So I think that there needs to be something about -- as this product goes forward, some kind of information included about what to do, what the symptoms are, and what to do if this occurs. Even though it might not occur with the indications we're talking about here, it's such a devastating event that it shouldn't take people by surprise.

DR. AVELAR: Certainly we agree. And we've seen this with a number of HA products. We've seen this including with fat injections. Anything that's being injected in around the face is at risk for this.

DR. LOCICERO: Yes, Ms. Timberlake.

MS. TIMBERLAKE: Sharon Timberlake.

I'd just like to add to Dr. Miller's point. It is one of their first warnings in their physician instructions for use. So perhaps if there's any publications available on this issue, that perhaps the company can think about stating that, referencing that article under that specific warning to help

address the users, make them more aware.

DR. MILLER: I think that would be important, and even the steps to take. And it's really an alertness thing because, when you first see this, it seems like -- it just seems very sudden. It didn't happen immediately. I mean, the patient just has persistent pain and swelling and it looks like every other thing, but then, pretty soon, it starts to necrose and it's all reversible with hyaluronidase. But if you don't know that's what's going on early enough, you can't stop it. So I think some increased visibility for the possibility of this problem, I think, is important.

DR. AVELAR: Again, we would take your recommendations, and we would be very, very open to any ideas to further fortify the label.

DR. BURKE: I just wanted to point out -- Karen Burke -- that if that were to happen, usually you would see immediate blanching. So I guess the warning should say, if there's immediate extreme blanching, then obviously the injection should stop.

DR. ALAM: Murad Alam.

That's very true. But to your point also, the next day you need to be vigilant. So if a patient were to call, you know, sometimes a patient is anxious after any procedure, but in this case those calls can't be dismissed because those could be indicative of the onset of this.

One other thing pertaining to -- you asked for potential strategies to avoid this -- might be clarification when it comes to, potentially,

labeling. At least the FDA summary referred to -- I don't want to get this wrong. One of the sites of injection was supraperiosteal, if I recall correctly, and supraperiosteal would, by definition, be submuscular, which opens the question, should this be injected intramuscularly? And I think that might be something that needs some clarification because there are various issues that are entailed in injecting a viscous substance into the muscle that might have a different side effect profile than subcutaneous injections and that might potentially predispose to a different adverse event profile.

So I'd be curious as to, in your instructions, are you suggesting subcutaneous injection, or if not that, then right above the periosteum? Or is anything in that range considered acceptable, from the subcutaneous all the way down including the muscle?

DR. AVELAR: So in the proposed IFU language that we have right now, it incorporates the area that was studied, which is deep subcutaneous supraperiosteal, to your point, and even intramuscular. So these areas, depending on what tissue plane you are, we felt that we've incorporated the three.

DR. ALAM: In terms of adverse events based on the depth of injection.

DR. AVELAR: And, again, we didn't, but with the caveat that everybody was injected subcutaneous and supraperiosteal. So it would be everyone got the mix of the two.

DR. LoCICERO: Dr. Olding.

DR. OLDING: I just have another question about the masses that required injection of hyaluronidase at the end, of the two patients. That's two out of 208. I've had one patient over the years that's had something similar to that, and that also is very devastating for your practice. And I think that we've been given the impression that the rate of complications is very similar to the other HAs. But I don't recall a percentage of that approaches 1% of granulomas, whatever you want to call these things, is the same with the others. I think it's much less than that. Is that correct?

DR. AVELAR: You're specifically calling out those two delayed onset phenomena. Yes, those two events we've called out specifically because they were the serious adverse events.

Probably the easiest way to try and answer that question is that I can show you the Juvéderm, where we had the first two-week diaries, and this product, where we had the first two-week diaries. It's not quite on point. But if we looked at most of the adverse events, if you will, they're common treatment site responses that carried over. Most of the events that happened with patients were common treatment site responses.

DR. OLDING: I'm not talking about the others; I'm talking about these two particular events.

DR. AVELAR: That's correct.

DR. OLDING: And I don't think that you have nearly as many of

that in the other products.

DR. AVELAR: That's correct.

DR. OLDING: Then I have to ask the question, why do you have so many with this product?

DR. LoCICERO: So many being 1%.

DR. OLDING: It's not one, it's less than 1%, but to me that's a lot. I've had one since I've been using Restylane.

DR. AVELAR: Perhaps if I can offer the history, I can give you the history to the background of those two patients, that may help.

We certainly know that with fillers, and particularly any HA filler, we've seen that there can be a delayed onset event. These two cases specifically, each one had an interesting story.

The first, one gentleman who was injected was asymptomatic and about six months later was playing golf, suffered a scratch in the cheek area, and it became infected. It was diagnosed with cellulitis. The individual was treated with antibiotics, but it progressed. So the underlying assumption was that there was probably a biofilm and etiology. That patient was reversed with hyaluronidase, antibiotics, and steroids, and it resolved without sequelae.

The second individual, it seems like it was infectious in nature also, potentially a biofilm type. Again, she was injected. There were about six or seven months that transpired completely asymptomatic. And then, a

day or two before, she had severe myalgia and arthralgia, something that seemed systemic, and then the nodules erupted and came up. Again, she was eventually reversed with -- oh, I should mention, during the course of the workup, she was biopsied, and interestingly the biopsy was clinically near normal. There were some histiocytes, there were some lymphocytes. There was no granuloma, there were no eosinophils, and there wasn't really any inflammation in around the area. Nonetheless, that patient was eventually treated with hyaluronidase, steroids, and antibiotics, and it reversed. Now, the sequelae was the biopsy that we had done.

DR. OLDING: I will again make the point.

DR. AVELAR: Understood.

DR. OLDING: Based on your numbers, there are more than in the others, so I don't think it's comparable.

DR. AVELAR: No. And what we've proposed in the proposed label is we'd like to call out those incidences that took place. We have a denominator within the study, and what we're proposing is we actually call out the incidents with what happened at the time and how they were treated.

DR. LoCICERO: Does the Panel have additional questions for the Sponsor and the FDA, anybody from the FDA?

DR. MILLER: I have another question for the Sponsor. The one complication you just mentioned gets my attention because it appears that

this may be acting like a foreign body. Then a patient gets an infection, a superficial infection or injury to the skin, and it can get secondarily infected.

Do you think that that's a reasonable sort of explanation? And if that is so, is there some sort of precautionary thing that should be done in patients who have eczema or some kind of chronic breakdown of their epithelium where they can get infected, and infected as secondary thing, or a warning about scratching your face or in shaving or whatever? Is that necessary, do you think?

DR. AVELAR: I mean, it's an excellent question. Certainly we're becoming much more sensitized to the concept of any HA filler and biofilm. There's a recent article by Bailey and Jeff Kenkel of UT Southwestern that speaks to a lot of these delayed onset nodules that happen with any fillers potentially having an infectious etiology. And maybe to your point. We need to be very concerned about aseptic technique. And perhaps if people have some sort of infectious process, should we cover them with a prophylactic antibiotic or not?

DR. LoCICERO: Dr. Alam.

DR. ALAM: Thank you.

Along those same lines, I think that's an excellent point. Why do they get those nodules? When you gave them hyaluronidase and you gave them antibiotics, I understand that problem resolved. Typically with other hyaluronic acid derivatives that have been approved, the hyaluronidase works

very swiftly, in a day or two if it's been recently, if the hyaluronic acid was recently injected, sometimes a little longer, and often might require multiple injections if the hyaluronic acid was injected many months ago and then you were trying to make it resolve.

Can you comment on the time to resolution or time to disappearance of the nodule from the point of injection of hyaluronidase? And did it require multiple injections of hyaluronidase? And was the profile, the timing of it going away, different than that for the other HA fillers that you have?

DR. AVELAR: Certainly. It took longer than what you describe. And each event had the same common theme, and that was it took a while before they actually got to the treating investigator to start using the hyaluronidase.

The first patient, the one that I described with myalgia and arthralgia, she became symptomatic at the beginning of August and did not start hyaluronidase until October, about the middle of October, so there was a certain amount of momentum. And then, in discussions with others, she probably had -- the dose that was being used for the hyaluronidase was probably too low. It was about 10, 15 units.

The second case, the same thing. The individual who had the scratch went and saw his primary care, then went and saw an ENT person, and it took a while before they got to their treating investigator.

I followed up with, in particular, the latter one that I described, and asked the same question and the answer that I got from him -- because this product is approved in Canada, it was a Canadian plastic surgeon. The answer that I got was, when you identify these, if you think that these should be reversed, you should treat immediately. That's the first caveat. And if you do treat immediately, they respond much quicker. And what he also noted is, typically, you would use a higher dose of hyaluronidase than with the other gels.

DR. ALAM: So did they require multiple injections in those two cases?

DR. AVELAR: Yes.

DR. ALAM: Can you guess as to how often they were injected --

DR. AVELAR: Yes.

DR. ALAM: -- and how long it took until it went away?

DR. AVELAR: I don't remember exactly. The first one was being treated with 10 to 15 units per lesion, and that went on for a few months, and the same thing with the second one.

DR. ALAM: Thank you.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I have one other question, and it's about the patients that did drop out or did not return for a touch-up, and I wondered if there's any correlation of those, if those patients had more adverse events or

adverse outcomes in the first 30 days or adverse events later. Was there any correlation of the people that did not return?

DR. AVELAR: Okay. And if I can, just because I know we've created a little confusion, I just want to be specific about the term touch-up. I want to make sure that I understand your question.

So there are three injections, if you will. There's the initial, there's the touch-up, and then there's the repeat that's available at 24 months. So there's the initial injection, and then the patients who had the touch-up, that represented 80% of the patients. Only 20% didn't. And then the primary endpoint was at six months, and then the trial went on. And then after 12 months, if you lost correction, you were eligible for a repeat treatment. And once you completed the entire 24 months, then again, irrespective of your status, you were eligible for repeat treatment.

So I'm assuming your question was of the ones that didn't have the repeat treatment.

DR. BURKE: Well, sort of for both.

DR. AVELAR: Okay, sure.

DR. BURKE: I mean the touch-up and the repeat treatment --

DR. AVELAR: Sure.

DR. BURKE: -- at six months.

DR. AVELAR: So there was no correlation with the touch-up. Patients were deemed to need a touch-up by the treating investigator. That

didn't enter into the equation in terms of I don't want a touch-up because of an adverse event.

In terms of the fallout, I don't have the specifics broken out of the patients who left the study, not getting the repeat treatment. I know some withdrew consent, but I can certainly see if I can get that for you. But I don't believe it was for adverse events. Actually, if I can share this with you, this may answer your question.

So this is device-related adverse events by repeat treatment. So the bottom line represents patients who had a repeat treatment, and the upper are the patients who did not have a repeat treatment, and the adverse events are about third for both.

DR. LoCICERO: Dr. Alam.

DR. ALAM: Sorry, I think I'm like a broken record. I have a question, multi-part, about the scale you used, the MFVDS. And I don't want to beat up on you. I understand that there's not much out there. I do similar sorts of research. It's very hard to find something that people can understand, that they can be consistent about.

But can you still give us a little bit more information about how the validation process for that unfolded and what exactly it entailed? And do you have any explanation for the small number of instances in which there were very wide differences between raters?

And often it was a one- or two-point difference, but there were

at least some instances when they were four points apart on a five-point scale, and I have some difficulty understanding that.

Thank you.

DR. AVELAR: Certainly. Let me ask Dr. Todd Gross to respond to this.

DR. GROSS: Thank you.

So the scale was actually validated twice. And I'll put up a couple of slides to sort of walk you through that process.

First of all, it was developed in consult with dermatologists knowledgeable with treatment in this area. Images were reviewed. Over 300 images were reviewed for potential prototypical images, and then verbal descriptions were created for each of the six grades.

In the initial validation, nine raters looked at 20 three-dimensional images. They also rated 18 live subjects. And then they did this in two sessions, one in the morning, and then in the afternoon they repeated their ratings for the images and for the live subjects. We calculated the traditional measures of inter-rater and intra-rater agreement, and we saw adequate level of agreement, that is, greater than .6, in all cases except for the second round of rating for the live subjects. It was at .5.

These results were provided to the FDA, and on the basis of their review, they asked for a couple of things. One is they asked us to define the three facial subregions and to validate the scale for use in the subregions.

They also asked us to expand the time frame between the two rating periods, from a morning and afternoon session to two weeks apart. And then third is they acknowledged that since the ratings were lower for live subjects, that the revalidation could be done with images. It's a challenge to get the same subjects and the same raters together two weeks apart, so the revalidation was done with images. But on the basis of these results, they suggested using two raters during the study and taking their average.

So the second revalidation was 61 raters. And this was used not just to revalidate the scale but also to qualify all of the treating investigators and evaluating investigators for their participation in the study. So now we had 61 raters, including all 15 treating investigators and all 30 study evaluators. They rated 22 pairs of images as clinically different and then -- that is, they looked at a pair of a subject's images and said that was or was not clinically different in terms of mid-face deficit.

And then, in a subsequent session, they rated all of those images plus additional images presented one at a time, and they gave them MFVDS ratings. And then, two weeks later they gave additional individual ratings for all of the images. So on the basis of this, we had both indications of clinically different and we had MFVDS ratings in two sessions.

So when we calculated measures of agreement for the revalidation, we saw, again, above the .6 threshold for intra- and inter-rater agreement. And on the basis of this, we deemed that the scale was valid for

use in the study with the provision that during the study, live ratings by evaluators, there would be two evaluators and that their results would be averaged.

So when we looked at the actual performance within the study -- and again, each site has two evaluating investigators, so we can compare their ratings for any given subject -- we did see exact agreement in 52% of the ratings. Now, these are for ratings that are performed between baseline and Month 6, which is considered the primary endpoint of the study, the primary follow-up period.

And as Dr. Jones walked you through, there can be instances where the absolute number given can be different between the two raters. And so here what we saw is the weighted kappa is .62. Now, the FDA actually presented a version of this where they compared the low rater to the high rater, and that actually inflates kappa a small amount, so they reported .65. But, again, the performance here is consistent with what we would've expected on the basis of the validation study, given that we're now moving to live ratings, and it is adequate from our perspective, in terms of exceeding the .6 threshold.

However, the primary endpoint of the study is not the absolute MFVDS rating. It's actually the responder rate as measured by the change in average rating given for the subject at Month 6 versus baseline. So if there's at least a one-point improvement, then they're deemed a responder.

And within the actual study ratings, what we saw is that the evaluators agreed as to the responder status of the subjects 75% of the time. That is, they either both gave MFVDS ratings that qualified them as a responder or they both gave them MFVDS ratings that qualified them as a non-responder.

So when we take this together, we see actual performance of the scale in the trial that is very consistent with what we expected from the validation studies, and we see a very high rate of agreement on the primary endpoint, which is responder status within the trial.

DR. ALAM: There still are those few cases that are very wide apart, and there are only 16. Thank you for showing that slide, but something is odd. I wonder if those are transcription errors. I wonder if those people, looking at those things again, would come up with that or they just wrote it down in this column instead of that column. It seems odd.

DR. GROSS: Thank you. That was the second part of your question. If we could have the percentage by exact agreement and one-point agreement, I'd like to show that slide again.

We did look at some of the individual cases, and in particular, we looked at the two cases where there was a four-point agreement. One of them appeared to be an inversion of the scale. And, of course, we looked also at the GAIS, the Global Aesthetic Improvement Scale. So in one case, there was clearly an improvement on the GAIS, but there was an MFVDS

rating at follow-up that just did not correspond to that. That looked to be a transcription error.

In the other case there was not a clear understanding of how this could've happened. I mean, it is not so clearly a transcription error but rather some bouncing around of the numbers. There's always the possibility that although they were adequately trained, they may have at one point simply misunderstood which number meant high and which number meant low.

As for the three-point differences and the two-point differences, we didn't see sort of a clear indication that these were all transcription errors. There simply did appear to be some cases where there was a difference of opinion.

Also I believe we mentioned previously that there was one evaluating investigator that appeared to be giving substantially lower ratings than all of the other investigators in the trial, and they were very different from the other evaluator at their site and all of the other evaluators. So that's actually responsible for a number of the two- and three-point differences.

DR. LoCICERO: Dr. Ballman.

DR. BALLMAN: Just a follow-up on the endpoint question. It also seemed to be that there was a lot of variability by site, and is there any sort of explanation for that?

DR. GROSS: So are you talking about site-to-site differences in responder agreement?

DR. BALLMAN: Yes, yes.

DR. GROSS: Yeah. So we did observe that there were differences in response rate by site. There were two sites in particular that appeared to be somewhat lower than the others.

So here's a cascade plot of their responder rates. Site 0706 was the site that had the one evaluating investigator. I mean, we obviously saw these results. The FDA observed that there was a univariate difference here, a statistically significant difference among sites. Researching that site, we did see this one evaluating investigator that appeared to be lower. And you see here the response rate at Site 0706 is 12.5%. The other evaluating investigator had a responder rate of 68%. So that appeared to suggest that it was due to an outlier.

And if can I add one more thing. So as a post hoc analysis, we simply removed that one evaluating investigator from the study and then analyzed the site-to-site differences. Once we've taken that one EI out, the site differences can be accommodated by volume injected differences.

DR. BALLMAN: That was going to be my question.

DR. GROSS: Yeah. And so when we enter volume injected into the model, if we remove that one evaluating investigator and we enter volume injected into the model, we no longer see a significant difference

across sites beyond what can be explained by volume injected.

DR. AVELAR: If I can clarify, perhaps, with the topic of MFVDS, if I can maybe clarify a question that was going on earlier about the subject, MFVDS versus the EI and the slide. The subjects were given -- if I can put the slide up just to straighten things out for everybody. The subjects were given the same MFVDS scale to look at. In hindsight, it was probably not fair to ask subjects to grade themselves on a clinical scale. For instance, they can't do a Munson (ph.) view and they're probably not intimate with convex/concave or being able to identify underlying musculature.

DR. LoCICERO: Does the FDA have any follow-up from this morning that they wish to add?

MR. VAN ORDEN: My name is Alvin Van Orden. I'm the statistician.

I'm just not sure I completely am in agreement with what the Sponsor just said about the one evaluator being completely responsible for the differences between sites, and that that one evaluator, even in that one site, there were instances where he rated a subject higher than the other evaluator. But we do recognize that there are differences between evaluators and between sites, and that is part of the differences we see. But I don't think that completely explains the difference.

DR. LoCICERO: Okay.

DR. AVELAR: So we agree with the FDA. What we were trying

to explain was that one evaluator, if we remove the one evaluator, the site goes from 12 to 68, post hoc analysis. But what we also tried to introduce was, there was another factor at that site, and one of the things that's interesting is we realize there's an average of volume used in the trial. If we look at the average responder, the median volume used is 7.2. If you look at the average non-responder in the trial, the average volume was 4.2. If we look at the volume used at that site, it was 2.65. So we agree with you.

DR. LoCICERO: Okay, we will now begin a portion of the meeting where we, as a Panel --

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. LoCICERO: No, we need to move on to where we deliberate amongst ourselves. I want to open the floor to the experts around the table to begin deliberating on any issues that you may have with any data that you've heard today. And this is a discussion among ourselves at this point.

We will now begin the portion of the meeting where we, as a panel, will deliberate amongst ourselves. I want to open the floor to the experts around the table to begin deliberating on any issues that you may have with any data you have heard today, either from the morning panel presentations, the discussions with the FDA and the Sponsor, or the material that you have read.

We're open to anybody to begin.

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Maybe since we have a new formulation and a new site with a new scale, that we need to redefine the term "getting work done."

Anybody want to start?

DR. ALAM: Can I start?

On the Executive Summary, I just want to point this out, we didn't discuss this much. On page 25 of the Executive Summary, Figure 7b -- and I'd love to hear a statistician's opinion on the intention-to-treat analysis and basically the data imputation scenarios for the six-month responder rate.

Not to be a pessimist, but in the worst-case scenario, it seems like the confidence intervals almost overlap just a miniscule amount, which would be the second from the bottom. Now, I doubt the worst-case scenario actually occurred, but I'd be curious as to the significance of that.

UNIDENTIFIED SPEAKER: The FDA --

DR. ALAM: Yes. The Executive Summary, FDA, page 25, Figure 7. Second thing from the bottom, worst-case.

So I think they're trying to deal with the dropouts and assuming, in the worst case, that all of the controls got better and all of the treated patients who were lost to follow-up got worse, hence looking at the worst-case scenario.

DR. LoCICERO: It's going to take a little while to figure that one out, I think.

Any other comments?

Dr. Miller.

DR. MILLER: I think that the Sponsors have a difficult two tasks to do. One is to demonstrate the effectiveness of the device, but the other is to create, de novo, an objective way to measure effectiveness with this aesthetic procedure. I mean, there's not ones you can go pick off the shelf that we all trust and believe. Most of these aesthetic procedures are kind of informally evaluated and not very rigorous.

So I'm very happy that we're trying to approach this rigorously, but I think we have to be careful about depending too much on the effectiveness studies that have been developed for the purpose of this proceeding because this is an evolving science already, and I think, you know, we may be able to find gaps in the studies that have been presented, but I think that's more a reflection of the evolving nature of this field, not necessarily a serious question about whether this device can fill out parts of the face.

DR. LoCICERO: And that may be something when we discuss potential post-approval studies -- Dr. McCauley has already mentioned the one -- possibility of another measure of evaluation that's been published.

And then, Dr. Burke, would you mind just going over that again with the silicone mask?

DR. BURKE: Yes. So I have two comments apropos to this.

One is that the cosmetics industry makes silicone imprints of

small wrinkles, and I think you could make a silicone imprint of the defect, and then at the six-month period or the one-year period or whatever, make another silicone imprint, and these can be volumetrically analyzed by standard techniques so you can see the volume difference.

So for wrinkles, the cosmetics industry measures the depth of the wrinkle, the length of the wrinkle, and the volume of the wrinkle. So in this case, for instance, you could measure the kind of volume difference from a silicone mask, which is real. So I think that's maybe a more quantitative perspective.

And then the other thing is, I think the suggestion that was made earlier about having -- instead of a no-treatment control, there are published papers saying that if you just inject saline, you get healing and fibrosis. And perhaps that would be a better control, to just have a sham injection and just see if that is -- I mean, compare that to a no-treatment control.

DR. LoCICERO: Again, we're discussing cosmetics here, and there is an important but almost indefinable area of self-esteem, et cetera, improvement.

Ms. Strong, you might want to make a comment concerning that.

MS. STRONG: I will make a couple of comments, as the Patient Representative.

I agree with what Dr. Miller said, a lot of attention on the MFVDS scale, and I cannot fathom how you could ever come up with a scale that would properly measure, from everybody's perspective, what the deficiency was. I mean, if you had every age range, every gender, every ethnicity, and had the same six scales, maybe, but I mean, that would be awful intensive.

I think it's very important when they're talking about the patient satisfaction on the GAIS scale -- and to me, it seems like patients were, for the most part, well pleased. And I think that when you're gauging that -- I mean, because I look at some of these pictures, and I think I can't tell a difference, but then the patient's pleased because they look at that defect every day. And so I think that it's very valuable to hear what they say even when we're trying to measure these things that are very, very difficult to measure.

I do have to say, on using the saline injection as the control group, I listen to all these people say that it's not painful. I've had those injections and they are -- I hope these aren't. But they're painful. I can't imagine a lot of willing volunteers saying yes, I'll participate, go ahead and inject me with nothing because I think the motivation is actually "get some improvement."

Two other brief comments, and then I'll be quiet unless you have questions. What I do feel with this product, in general, is that even the

adverse events -- and we've talked a lot about them -- that they're not disfiguring and they're not -- we talk about them being disabling, but I don't get the disabling piece of it. I mean, you may have bruising, you may have a lump or a bump that you can feel, but they're really not visible, and I don't feel like they impair daily activity. Maybe you're sore for a day. But beyond that, the adverse events haven't seemed as major as we talk about them. And, of course, I come from a different arena as a patient representative, so that may not be a fair assessment in this venue. So tell me if it's not.

Thank you.

DR. LoCICERO: We appreciate your comments.

Ms. Timberlake.

MS. TIMBERLAKE: Sure. Sharon Timberlake.

I just want to comment. For the last 10 years, I've focused in light and laser aesthetics and worked on probably over 100 studies, and there are not a lot of validated scales out there in the aesthetic world, as we all know.

I got a comment on the MFVDS scale, that I think they did a very rigorous validation study looking at the intra-observer variability. They had a very large sample size with a number of photos they evaluated and the number of evaluators. So my opinion, coming from the industry, I thought they did a nice job validating that scale.

Number 2, it is aesthetics, to your point. Considering the

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patient benefit is, to me, also a primary endpoint with level of satisfaction, and at the end of the day, if it's proven safe and effective, is up to the physician, through conversations with a potential patient they're treating, as well as the draft labeling that we've been reviewing from the physician and the patient information brochures that they produce that shares the information about the benefit and risk information.

My only comment on the patient labeling is that they consider including adverse events < 5% in the patient material. And talking more about month of resolution to help give the benefit/risk profile information to the patients.

DR. LoCICERO: Dr. Ballman.

DR. BALLMAN: So just to go back to comment on the figure for the worst-case scenario. The control group does cover -- the confidence interval does include the 70% mark, so it went past on that for the worst-case scenario. However, it does look like there probably is a significant difference between the treatment group and the control group, so I'm comfortable with that.

And then having to say more, I do agree with the fact that the patients seem, on their scales, to be very satisfied. Even though I think this is an imperfect measure, I am uncomfortable with the fact that many of the disagreements are one point between the raters and one point is considered clinically meaningful. So I think that there has to be, moving forward in this

field, an improvement upon this instrument, but if it's the first of its kind, I think it's doing pretty good. I mean, within quality of life and cancer, where I come from, it took a while to sort of get those scales right, and so I think, in general, everything's moving in the right direction of all the measurements they've done.

DR. LoCICERO: Ms. Mattivi.

MS. MATTIVI: To reiterate what's been said about the difference between -- or the balance between trying to quantify something that is also an aesthetic. We heard from some of the people that had undergone this procedure that they were looking for something subtle, that they weren't looking for the dramatic change. And so what might be quantified as a one-step difference in the scale may have been more than what they were looking for, actually. So I do think that that balance between -- more is not always better in terms of patient satisfaction.

DR. LoCICERO: I get the sense, from looking at all of this data, that in general, there are a lot of patients who are desirous of having something done and that, in general, physicians who use products like this are desirous of having good results, and that there appears trouble on both ends of this, that if there's too little volume that's necessary, that you can overshoot in one direction or the other, and that if there is a large volume, that one can get more adverse events. And we kind of have a discussion about the ends of this group and maybe that would speak more toward the

potential for labeling.

Dr. Alam.

DR. ALAM: No, I see exactly what you're saying. We are kind of speaking in the sort of worst- and best-case scenarios, and I would echo what some of the other speakers have said about the medium scenarios. For a couple years of my life, I did develop questionnaire measures for a university, and while the measures in dermatology -- especially in fillers and injectable devices, they are very subjective. There are technical issues, and overall, the quality of the measures, quite frankly, is fairly dismal in that context.

I think they've made a pretty good effort to validate. It's not a perfect validation, but there are really very few scales that are even validated at all in this arena, and I think they've been very forthcoming in explaining all the problems with their validation and their ability to improve upon it. So I think I'm pretty happy about that.

The other issue was that of subtle effects, and I think, to some extent, that's true. But also keep in mind that photography really flattens everything out. So in my experience, when we've done filler studies, we think it's a dramatic effect without being just enthusiastic for the sake of being enthusiastic. We really do think technically it's a dramatic effect. And yet, when we look at the "before" and "after" photographs for publication, they don't look that different anymore, but when we saw the patient, there was quite a dramatic effect.

So based, at least on my experience, the differences in the computer generated images here are really quite substantial, and I think that's what we heard in the testimony from the patients, too, that while it might not be well conveyed in the images, they really got a pretty good effect for -- in most cases, in the average case, for minimal downtime, for minimal inconvenience, and for not those rare but worrisome effects.

DR. LoCICERO: Dr. Miller.

DR. MILLER: Yes, I appreciate those comments, and I don't think the Sponsor should be penalized because we don't have good tools yet. We need to get better tools, though, and I think, with precise image analysis, looking at very subtle differences -- the differences we see in real life are differences in shading and in things like this in the light; a computer can probably pick that up if a proper system was designed. I think that that still needs to be done. And the volume analysis as well.

I mean, there's a subjective piece with all aesthetic surgery, but whether there was an increase in volume, that has nothing to do with the aesthetics. There either was or there wasn't. And that should be able to be measured at some point. But I think millions of people have had HA injections, and there have been over 500 syringes of this injected. I know that's not -- I don't know how we can weigh that, but I mean, if it was not effective, there would probably be, like, 10 syringes injected, not millions or hundreds. So I think that's a valid consideration here.

DR. McCAULEY: Even if your validation process isn't perfect, it does not mean that you have not achieved some benefit. And I think that's a very important lesson to remember because these validation processes are going to change several times each year. And I think that that has no impact whatsoever on whether it's effective.

DR. BALLMAN: Can I ask a question of the Panel, being sort of naive -- new to all this? So how does the AE and safety profile of this filler compare to what -- alternatives that are non-fillers for people?

DR. LoCICERO: Dr. Chevray.

DR. CHEVRAY: Yes. In my view, there are certainly surgical options to facial rejuvenation, mid-facelifts, which is a surgery, and certainly compared to any surgical procedure, the adverse events listed here are vastly lower. And in my personal consideration of the data that's been shown today, these AEs, for example -- so for the 88 device-related adverse events out of the 270 patients, they were basically -- none of those adverse events negatively affected the physical health of the patient. None of the patients were disabled by any of these. The most serious of the 12 serious adverse events in the device-related adverse events was probably that infection, which required antibiotics and probably some down time in the hospital or clinic visits by the patient.

So, again, my overall view -- and when you perform surgery, you can really harm the patient and I have not seen -- I don't really see any

patients being harmed here. As Dr. Miller said, there are of sporadic reports with any injectable, that you can introduce this into an artery and cause necrosis of tissue or it can get into the central retinal artery and cause blindness, but those are very rare reports.

DR. LoCICERO: Dr. Olding.

DR. OLDING: I hate to sound like Mr. Negative here, but I really think the major reason that we're having all this discussion is because we don't -- we haven't had a proper control. If we had had another HA as the control or something else, much of the discussion, I think, would be not centered around the evaluation technique. Having said that, I think it's as good as you can get, and I applaud them. I think you did a good job for doing it.

But I want to bring up something slightly different, and that is in a way, we're comparing what's happening in this area with what has gone before, which is injections in other areas, which are a lot different. I have patients who have had HAs in for five years -- not volume, obviously -- and they're definitely there for five years and particularly in the malar areas. I don't know why. Maybe because it's less movement up in the tear trough. They go on forever, it seems. And in the nose, that's totally different than in the lips.

So I don't know how to evaluate this product in terms of duration compared to the others because we're doing it in a totally different

place. And I wondered if other panel members had any ideas about that or experience with it.

DR. LoCICERO: Anyone have any other experience?

Dr. Burke.

DR. BURKE: Well, I think this duration seems longer than the other Juvéderms that I've used. Of course, I haven't quantitated it in my own practice, but I think when -- I usually see patients about once every nine months or year or every year and some people every two years. So you're right, it's difficult to quantitate, but it seems as though overall this is longer-term correction than the present hyaluronic acids that are used.

DR. LoCICERO: They're also injecting a lot more.

DR. BURKE: That's true. Absolutely.

DR. LoCICERO: Dr. Miller.

DR. MILLER: I think another pointer is that the rate of absorption is related to how well vascularized the space is, so the injecting into these fat compartments in the face, I imagine they're less well-vascularized than, say, immediately below the dermis or something. So I think that may also be one reason why that one patient had an infection.

What's gotten my attention here today that I think we should think about, making sure that it's labeled clearly, is the risk of an infection if you have a breakdown of the skin. I think that needs to be alerted. And also, I think just in general, for all the HA fillers, it needs to be more clear in the

labeling that the risk of intravascular injection is something to be mindful of. And it's more than just saying don't inject intravascularly because there's a whole host of things that you shouldn't do all the time, and you sort of, like, glaze over when you see the list. But this is extremely important because the results, if you do inject it incidental intravascularly, can be really devastating.

DR. LoCICERO: And just to emphasize the point about infection, it doesn't matter what the device is that you're putting in or injecting, any potential for infection, even when there's the minutest amount of bacteria, can result in disaster months or years later. So clearly it's an issue that we need to address if we're going to talk about labeling.

An issue that we really haven't talked about much is this particular study, the upper cutoff was 65 years. There are going to be a lot of patients older than 65 who are going to be desirous of this.

Anybody want to address that issue?

DR. ALAM: I think that's a very good point, and as I mentioned earlier to the company, I believe there are also other issues. I think HIV patients are going to get this because they have tremendous mid-face atrophy, and that's a major, major problem and they were specifically excluded.

So that might not be within the scope of the labeling; I don't know if it is or not, but I think HIV patients, older patients, and even some of the other populations, patients with other skin types, who were included in

this study were really not included in the study in large enough numbers for the subgroup analysis to be significant. So I think it would be useful to track those going forward. Also, as Dr. Olding suggested, in the context of the fact that we are putting a lot more volume a lot deeper. So assumptions we know to be true for other HAs wouldn't necessarily hold up exactly the same.

DR. LoCICERO: Dr. Olding

DR. OLDING: Again, going back to durability, I don't think I really understand this. Why were two-thirds of the samples tested? Did they show no product, two-thirds of the biopsies, if it's meant to last 21 months? Two of the biopsies are the biopsies that were done, I think, at each of the time levels. How is it that it can last 21 months in one location, and in two-thirds of the samples, there was nothing?

DR. ALAM: I think I can -- I'm sorry, go ahead.

DR. BURKE: I was just going to say, on the first studies we did with collagen, with bovine collagen, we found that the bovine collagen injected disappeared -- the foreign collagen -- and it's replaced by collagen, by natural collagen. So it's sort of that particular implant was kind of a scaffold for new collagen to form, and that's why I mentioned the possible control of just injecting normal saline, which the pain is not the stinging of the implant, which often the hyaluronic acid might hurt more than saline, but you still have the pain of having a needle be deep.

But just creating an injury creates healing, which creates

fibrosis, so possibly the stimulated natural fibrosis over the HA implant, although we think the HA works by imbibing water and staying there. So I don't know if they did antibody immunofluorescence kind of studies to see -- I mean, new collagen is Collagen Type III rather than the normal Collagen Type I. So that could potentially be studied.

DR. ALAM: And along those same lines, I agree with everything Dr. Burke said. I've done some of these studies, myself, and I think there are two potential considerations -- don't know the answer to your question, but two potential considerations.

First of all, HAs are abundant in normal skin, and the turnover is very, very rapid. So if the product becomes widely dispersed, it's very hard to tell from the background. And really, when they're biopsying, unless there's one large clump of HA, it's hard to know if that's their HA or some other HA. And we've had this problem, too, in biopsying because it's really easy to miss the nodule. I think sometimes a nodule is firmer, and when you're biopsying it, you push it aside and it doesn't show up on a 3 mm pipe, so sampling error is another issue.

And then finally, as Dr. Burke alluded to, as I'm sure you know, there is some data indicating neocollagenesis that does occur. In particular, I believe, from Michigan in 2007, they elucidated the fact -- University of Michigan -- that the process of putting the injection in created some mechanical stretch that causes some native neocollagenesis. But I think

mostly, it's just a matter of it dispersing widely, and it's really hard to actually find a clump of any filler.

We've tried some other fillers that I won't mention on biopsy. And, in fact, in some studies, we've had to do multiple biopsies, like four or five behind the ear, to find anything at all. So I think that's a common issue with fillers, and so maybe the whole biopsy modality isn't terribly useful.

DR. McCAULEY: Is that age related?

DR. ALAM: Not as far as I know. I think it's related to time from injection. I think the first day or two or even a week, you can find it, but a week or two later, it's really hard.

DR. LoCICERO: I understand that there may be some additional data on the vasculitis question that we had from before. Is there any further information on global experience concerning the issue of vasculitis? It was mentioned that there was the glabella injection and the nose injection. Are there other instances that the Sponsor knows of?

DR. AVELAR: There are no incidences of vasculitis that I know of other than the nine line items that were referred to, which were five subjects.

DR. LoCICERO: Outside of this study, though --

DR. AVELAR: Those are the postmarketing -- I'm not aware of any vasculitis.

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. AVELAR: No. There were no other occlusions of other vessels. The only two we're aware of is from the glabella injection and the nasal injection.

DR. LoCICERO: Okay. I think we've kind of gotten that subject about as exhausted as we can get. Additional comments?

Again, I want to go back to this idea of the older patient. What sort of guidance should a physician have concerning patients over 65 who are desirous of this sort of injection?

Yeah, Dr. Miller, let's start with you.

DR. MILLER: I think this is where a clinical judgment thing comes in, the part of the physician. There's a limit to how much you're going to accomplish with a filler, and often, as patients get older, to rejuvenate their face, they require more than fillers. They require actual movement of the skin and facelift and rhytidectomy and these things. I don't know if that should be addressed here, helping guide a physician with a judgment issue, but there are limits as to how much facial rejuvenation you're going to accomplish by simply injecting a filler.

DR. LoCICERO: Dr. Olding.

DR. OLDING: I will just tell you that with every facelift I do, I inject something. If it's not fat, then it's some sort of fillers. And so yes, I agree with you that you can't just pump in something ad nauseam, but once they've had a facelift -- and now that I'm getting older, most of my patients

are getting older as well, and most of them are 60-65. And you tighten up the skin, and then they still need volumizing, and I think it's on an individual patient basis, but I don't think that because you're 65 or older, over 65, you should have more of a problem, even though they weren't studied particularly in this group.

DR. LoCICERO: Well, let's kind of go around the table here.

Mr. Melkerson.

MR. MELKERSON: Just to make a point. We can only approve what is being studied. If you're looking at things outside, that may need additional data.

DR. LoCICERO: Understood. And I wanted to be sure that the Panel had -- if they were desirous of that sort of thing, we might give some guidance to the FDA. It sounds like we don't need to.

And sort of let's go around the table here.

Ms. Timberlake, additional comments?

MS. TIMBERLAKE: No, not at this time.

DR. LoCICERO: Ms. Strong?

MS. STRONG: I do have one, and I may have misunderstood this, and you all can correct me if I did. But is it my understanding that in this particular trial, that none of the injections were done submuscular, and if that is the case, then is that part of the approval or is it the other two levels under the skin? And you all can say the words.

DR. BURKE: I think that's one of the points I was going to make, that I think in future studies and in thinking about this, first of all, I think that everything presented was excellent and very excellently monitored. But it would be interesting to monitor the zygomatic arch versus the other two sites and to monitor intramuscular as opposed to supra just above the bone because I think that that's a clearly very different kind of technique and might have different adverse effects, as Dr. Alam mentioned, and also may be a different efficacy.

DR. LoCICERO: Dr. Alam, you're the one who asked the question concerning the position of injection. Maybe you could clarify that based on your understanding at this point.

DR. ALAM: Sure. My understanding is that there are several levels. So you have the skin, which is the epidermis and dermis, those are stuck together. And underneath that, you have the subcutaneous tissue, then you have the muscle and then you have some other space, and then the lining of the bone and then the bone. So it sounds like, in some cases, they put it right above the bone, and in some cases they put it in the subcutaneous. And then maybe sometimes they put it in the muscle, too, but that's not really referred to, but that's kind of in between the other two.

And so my question was well, if you actually inject the muscle directly, is it different, because it's very vascular, and does stuff get stuck inside it. And I think that's what Dr. Burke was referring to, too, and it sounds

like we don't know.

MS. STRONG: Yeah, you didn't make me real comfortable with that. You seem to be very leery of it being intramuscular, and that's what prompted my question because it sounds like there are concerns there. It's different from the other filler injections that I'm aware of.

DR. ALAM: Yeah, I don't think they were trying to inject intramuscularly, so maybe we should just specify that they shouldn't do that because we don't have specific understanding of what happens.

Can I ask one other question while I'm at it?

DR. LoCICERO: Sure.

DR. ALAM: And I'd like to ask the Panel's view because one of the other things that I would be worried about is if I thought this had a significant risk, more so than other Juvéderm products, of inducing eye problems, serious eye problems, like visual field defects and blindness. And at least, based on my understanding of the one case that occurred, it seems to me, given the eight months that elapsed between the injection and the time that happened and the fact that the person had some issue bilaterally, that it's really not consistent with prior reports like it's fat or collagen causing immediate or next-day blindness in one eye only with exquisite pain. But I'd be very interested in whether the rest of the Panel feels that that's related or unrelated.

DR. LoCICERO: Let's start with Dr. McCauley.

DR. McCAULEY: I guess the real question is how do you know that you're supraperiosteal or supramuscular? With your injection technique. To me, you can't tell. The only way I know that you can tell is if it's above the periosteum, you'd have to go down and hit the bone and back up.

DR. ALAM: Exactly, um-hum.

DR. McCAULEY: And that, in and of itself, can cause problems.

DR. ALAM: I think the only way you can be sure is if you hit the bone, like you said, and then withdraw, and people do that sometimes when they're injecting near the eye region or at least get close to the bone. And subcutaneous, I think, is just based on where your needle tip is. A lot of these fillers are referred to as dermal fillers, but as you know, there is clear certainty, I think, at this point, that there are almost always -- not this filler, but other prior approved fillers are injected, actually, in the subcutis.

DR. McCAULEY: That's what I asked before in terms of technique, you know, you may have to do more needle sticks than you would on another patient if you're trying to get subperiosteal or supraperiosteal. And, you know, you back out and you may get muscle but you think you're supraperiosteal. In fact, you are but you're not where you're supposed to be. And those are all technique questions, which we didn't address.

DR. LoCICERO: I think to some extent we need to depend on the expertise of the injector in those situations.

Ms. Mattivi, any additional comments?

(No audible response.)

DR. LoCICERO: All right. Dr. Ballman, any --

DR. BALLMAN: No additional --

DR. LoCICERO: Anything from this side of the room?

Dr. Chevray.

DR. CHEVRAY: Yeah, I agree. I think that one case of seven or eight months after the last product injection, Voluma injection, the optic nerve problem, I think I agree with the Sponsors, to classify that as unrelated to the device.

My one comment here, additional comment, I'd like to make is we've talked a lot about measuring the effectiveness of Voluma, and there is some question as to how effective it is because we don't know, for example, if the control group could have been better and might have had a higher response rate even in the control group they had with no treatment. But despite the questions of the effectiveness, my belief is that there is some effectiveness to this product, and even if it's not highly effective, I think the risks of having it injected are relatively low compared to other modalities of aesthetic improvement of your mid-face. My opinion is that that risk/benefit profile is fairly favorable.

DR. LoCICERO: Dr. Olding, any additional comments?

(No audible response.)

DR. LoCICERO: Dr. Miller?

(No audible response.)

DR. LoCICERO: Dr. McCauley?

(No audible response.)

DR. LoCICERO: Okay. I think we sort of have a good general feeling of where we are at this point, so it's probably reasonable that we take our break now.

Panel members, please remember not to discuss this meeting topic during the break amongst yourselves or with any member of the audience. And let's plan to be back here at 3:10 so that we can address the FDA's questions.

(Off the record.)

(On the record.)

DR. LoCICERO: At this time let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on data in the panel packs, the presentations we heard this morning, and the expertise around the table. With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription. The questions will be read by the FDA, and then we will discuss them.

DR. NIELSEN: The analysis of the VOLUMA-002 Study indicates that Juvéderm Voluma XC met the pre-specified primary endpoints for

effectiveness. Safety information was collected over the course of the study. Based on these data, Panel comment is requested on the following questions:

Question 1: Common treatment site responses (CTRs)

continued in 20.0% of subjects beyond 30 days becoming adverse events (AEs), and 78.4% of CTRs were identified as moderate to severe.

Device/injection related AEs were reported in 32.6% of subjects with most AEs resolving within 60 days. Please comment on the duration and severity of these injection site responses to Juvéderm Voluma XC, and their effect on the safety profile of this product.

DR. LoCICERO: In terms of beginning this discussion, I think we have two individuals that kind of represent the two ends, and we can have them begin our discussion and then go in between.

Dr. Chevray, maybe you can begin with your observations.

DR. CHEVRAY: Sure. Again, along the lines of what I said a little while ago, if you look at all of the adverse events or even the common treatment responses that were related to the device, that were deemed related to the device, there were really none of them that were certainly life threatening or that had any long-term sequelae. And I even don't -- I mean, I wouldn't call most of the treatment responses or a severe -- the term "severe" has been applied to many of them, but I wouldn't consider bruising to be severe.

DR. LoCICERO: Dr. Olding, I know you're of a little bit different

opinion.

DR. OLDING: Not entirely. In terms of the common treatment site responses, which continued in 20% of the patients beyond 30 days, that doesn't surprise me at all because we're injecting larger volumes. And the fact that there were -- 78.4% of the CTRs were identified as severe also does not bother me. I think the more you inject, the more you would anticipate those sorts of things, just on a volume-by-volume basis. So we don't disagree there.

But the only thing that I'm concerned about, really, is that percentage of granuloma, whatever you want to call those nodules, because I think it does make a big difference to the patient, and if you have a patient that's in public making a living every day, if they have a painful nodule that's red, inflamed, swollen, it is really a very problematic thing. So I'm expressing my concern about that 2% -- or I'm sorry, 1% of patients -- or almost 1% of patients who would have granulomas. Otherwise, I have no concerns.

DR. LoCICERO: Dr. Alam, do you have additional concerns?

DR. ALAM: I think they've all been well stated. My feeling is that, indeed, there is a proportion, as is clear in this question, one out of five patients who have some adverse events beyond the 30-day period, but that's probably related to the original adverse events, which are mostly pertaining to swelling, bruising.

Basically, you're taking a needle or multiple needle sticks and

putting several cc's of material into the subcutis or supraperiosteal and that just takes a while for your skin to heal. So I think that in one-fifth of the patients, it took more than 30 days for that to completely go away is not alarming, I think, as long as patients are aware that it's going to take a while for the swelling to go down. And given that there are really no cases except for those two slightly odd cases of people having persistent unremitting swelling as has been reported outside the U.S. with some permanent injectable fillers, I'm pretty comfortable with this.

And, again, as Dr. Chevray outlined, some of these events are called severe, but while they are in the context of this study, really are not severe compared to potential side effects of incisional surgery or other catastrophic, irreversible outcomes.

DR. LoCICERO: Dr. Burke.

DR. BURKE: I was just going to say exactly, kind of, that: That the adverse effects are not permanent and they are reversible, maybe requiring hyaluronidase. But I think that's a very important thing, that there are no cases of permanent disfigurement.

DR. LoCICERO: Dr. Miller, any comment?

DR. MILLER: I have none.

DR. LoCICERO: Dr. McCauley.

DR. McCAULEY: No, I agree with just about everything that's said. I'm not really concerned so much about the nodules and granuloma

formation because I think those are transient factors.

MS. MATTIVI: I think the other thing is just that, as I remember, the assessment, the categorization, was patient driven and not a clinical assessment of mild, moderate, and severe. So I think that needs to be taken into account as well.

DR. LoCICERO: Additional comments concerning this?

(No response.)

DR. LoCICERO: Mr. Melkerson, let me summarize here. I think that the Panel feels that there are some transient responses which do go away, that are not life threatening, that do not seem to be particularly important, but that there may be some low percentage cases that may be of significance in that these are low but require important identification to the user of the product.

Does this answer the FDA's concerns on Question 1?

MR. MELKERSON: Yes, it does.

DR. LoCICERO: We're ready for Question 2.

DR. NIELSEN: Question 2: With Juvéderm Voluma XC, CTRs and AEs have been shown to be more likely with higher injection volumes (9 mL or greater) and in older patients. Please comment on the safety of Juvéderm Voluma XC over the injection volume range used in the clinical study (1-13.9 mL, mean 6.6 mL), and comment on any recommended volume maximums or guidelines for use of this product if approved for marketing.

DR. LoCICERO: We have been talking about this to some extent, that the more volume, the more chance for difficulties, but we haven't really talked about a particular limit.

Does anyone have any feelings about this?

Dr. Alam.

DR. ALAM: I would suggest that we consider labeling it as it's already well explained in the FDA question, which is that AEs have been shown to be more likely with higher injection volumes, and we could even specify 9 mL or greater and in older patients. And I think just communicating the higher volume posing a risk might be sufficient guidance to both patients and injectors. I don't think we need to have an upper bound. I think that should really be left to clinical judgment.

DR. LoCICERO: How about the term "older patient," is there a specific number we should place or leave that up to the definition of the patient?

DR. BURKE: I think it suffices to leave it up to the clinical judgment. As we all get older, older is younger.

DR. LoCICERO: Dr. Chevray.

DR. CHEVRAY: Yeah, Chevray.

I agree with the other two panelists. Well, first of all, the study did not involve injections of greater than 12 cc's in any one injection and patients over -- or subjects over 65 weren't studied, so we don't have very

good grounds for placing maximums on either of those, so as the others have said, I would repeat just that there should be some warning that injections into older patients and greater volumes seem to have a greater risk for adverse events.

DR. LoCICERO: Dr. Olding, should there be some sort of stronger language when we're getting to those numbers?

DR. OLDING: No.

DR. LoCICERO: Well, that's definite.

Any additional comments in this area?

DR. CHEVRAY: Yes, I have one.

What about the exclusions of the thin-skinned individual? Should we not also include the fact that those patients were not included in the study and therefore they, like the elderly population, have not been studied, and therefore we don't know anything about that population?

DR. LoCICERO: I think that's an important point.

Does anybody want to further discuss that issue? Thin-skinned, older.

Yes, Ms. Timberlake.

MS. TIMBERLAKE: Sharon Timberlake.

I was just going to say maybe handling that information through a caution statement and leaving it up to the decision of the treating physician based on their analysis of the skin and the area that they're looking

to treat.

DR. OLDING: I forget how, but there are similar sorts of warnings in the other HAs and in many other products about -- I don't know exactly how it's written, but when it hasn't been studied, there's a disclaimer. So for all the things that have not been studied, there should just be a disclaimer. It doesn't have to be anything particular as long as it's in there.

MS. TIMBERLAKE: I'd just like to point out that probably handled through a caution statement or a warning and not a contraindication statement.

DR. LoCICERO: Okay, Mr. Melkerson. Concerning Question 2, I think the Panel feels that there are certainly issues with higher volume injection, older patients, and also the addition of thin-skinned patients.

But the Panel also feels that it is important that areas that have not been studied are stated: patients over 65; thin-skinned patients; patients with injections over large volumes, such as 12 mL, and that this should be handled as a caution to the user of the product.

Does this answer FDA's concerns on Question 2?

MR. MELKERSON: Thank you very much. It should.

DR. NIELSEN: Question 3: The MFVDS scale was validated by the sponsor. However, in the Juvéderm Voluma XC clinical study, evaluators often did not agree on the rating of given subjects. In addition, subjects reported a > 1 point improvement at 6-months in the MFVDS evaluation less

frequently than the independent evaluators (58% versus 85.6%). Finally, the no-treatment control group in the Juvéderm Voluma XC clinical study had a 39% response rate. Please comment on the impact of these observations on the validity of the MFVDS scale used in this study.

DR. LoCICERO: We've been sort of dealing with this issue all morning and early afternoon, but Dr. Ballman, maybe you could just sort of summarize this for us?

DR. BALLMAN: Yeah. And I would like to point out -- I mean, it's an imperfect instrument, but it's the best instrument available, and it appears to have been through a rigorous validation process, and so we feel comfortable with that.

Also, I'd point out that even though there was a response seen in the control group, the study met its primary endpoint using this instrument, and there was a difference between the control and the treated group.

And so I think I feel comfortable that they have established that there is some efficacy along with the secondary endpoints going in the right direction.

DR. LoCICERO: Dr. Miller.

DR. MILLER: I think the response rate in the control group may have been real because a person's hollowness of their mid-face could be improved with changes in their menstrual cycle or weight gain or being better

hydrated. I mean, you may have a more hollow face on a day that's hot, if you're in Phoenix and -- I mean, so it's hard to know how to interpret that, but I suspect there's probably some real changes that occurred.

DR. LoCICERO: Does the Panel have a feeling that maybe going forward, if the FDA were to get a different study from a different sponsor, that a different study could be developed with a newer evaluation?

DR. BALLMAN: I would say it would have to be validated, the -- has been validated, so I wouldn't want to go backwards. Any new instrument that gets proposed -- and I think there can be improvements made upon this instrument, but it should be validated to be used.

DR. LoCICERO: Dr. Chevray.

DR. CHEVRAY: I think it would be more important for future studies of this type to include a control group that uses a sham injection as opposed to no treatment whatsoever so you could run a double-blinded study. I think that would do more to create a stronger study.

DR. LoCICERO: All right, I think we'll be addressing that again in a little while.

Concerning Question 3, Mr. Melkerson, I think the Panel feels that, considering everything, that the Sponsor has done a very good job in developing an instrument, validating that instrument, and using that measure to the best of their ability and that possible future studies with other validated instruments might be useful, but that this was certainly the best at

the time.

Does this answer the FDA's concerns on Question 3?

MR. MELKERSON: Yes, thank you.

DR. NIELSEN: Question 4: The Juvéderm Voluma XC clinical study includes a blinded comparison to a no-treatment control at 6-months for the primary effectiveness measurement. The clinical study also includes effectiveness measurements without a blinded control for comparison from 9 to 24-months.

- a. Please comment on any limitations in the use of effectiveness measurements in the absence of a blinded control, and the ability for these measurements to detect clinically meaningful product performance in the follow-up period after the 6-month primary effectiveness time point.
- b. In this context, please comment on appropriate study design to evaluate long-term effectiveness for products of this nature and this indication for use.

DR. LOCICERO: Dr. Chevray, I think your comment is appropriate at this point, and we'll carry it over to our discussion here.

Any additional points on the control?

Dr. Alam.

DR. ALAM: I think that is a great idea because that would filter out a lot of the short-term effects like bruising and injection pain. I think,

also, with regard to this question, while they didn't have a blinded control for after six months, I think we can't completely discount the data after that point because as it's been discussed before, it's extremely hard to keep patients in studies for much longer than that. And they have some data going up to 24 months.

So with regard to labeling, I would encourage FDA to consider, or this Panel to consider, some way of taking that into account. It might be something like it's been shown to be this effective until six months and less rigorous data indicates some degree of effectiveness until two years. But I wouldn't just completely drop that out, and I think it's very difficult to suggest a better study that would really track this in a blinded fashion for longer than six months or at most a year. It's just impossible to keep patients in such a trial. The only way I can think of is if you had a very small cohort and then you tracked them for a longer period, very loyal, very reliable patients. But, of course, that would be more anecdotal than statistically valid.

DR. LoCICERO: We've been addressing this issue a lot, but patient recruitment may be somewhat tough.

Ms. Strong, would you reiterate your concerns about the patient side?

MS. STRONG: Well, I've been told that the injections without the actual product that are painful are the ones with, say, just saline. But I do think that there probably would be some increased challenge in recruiting

participants. I don't know, I've seen trials done in the past where they will follow up at the end of the trial with the medication that was being tested on the other side and that would be a potential piece of encouragement for people to put themselves in there.

But talking long-term follow-up with, say, the saline injection, I think that could be difficult. But, I mean, I'd be game as a patient, but I don't know how many -- I'm a pretty good sport, but I don't know how many people I can see being convinced that they should participate as well.

DR. LoCICERO: How about from the Sponsor's standpoint, Ms. Timberlake?

MS. TIMBERLAKE: Sharon Timberlake.

I understand some of your concerns with studying the primary endpoint, but we also have to consider, again, it's aesthetics and it's not just one evaluator looking at these patients long term, so I think that holds a lot of weight with the two evaluators and the principal investigator coupled with the patient data, the additional 3-D photographic measurements, that that coupled together truly does support long-term effectiveness given the situation of trying -- from some sort of long-term control group.

DR. McCAULEY: It's the fact that this was a 5.3:1 protocol for the study. And what are the advantages of having it 5.3:1 versus 1:1 patient accrual?

DR. LoCICERO: That's a valid point, particularly in a situation

where this is a popular procedure and that recruitment, in general, may be a little easier. In some trials where the treatment is more specific and the population smaller, a 5:1 ratio randomization might be useful. But even in some of those situations, 3:1 has been used rather than 5:1.

So any other comments concerning changing the ratio for treatment versus control?

DR. BALLMAN: If this were an active control, I would be very uncomfortable with the 5:1 randomization. And any studies going forward, if there can be an active control arm, I would advocate for that, something that's been approved, but that was not the situation here. But in terms of not having an active control to give these patients, it is a little unusual to have 5:1, but I think it made their recruitment a whole lot easier.

DR. McCAULEY: Juvéderm without lidocaine is another protocol that was about 5:1.

DR. LoCICERO: Additional comments?

Dr. Miller.

DR. MILLER: I think if there is some contribution of just the injection without the HA to the result, without a method for measuring the outcome that has a greater resolution, you know, will just make this study more difficult to interpret. I think "no treatment" is a much more clear, sort of like, option than if you do anything which might affect the contours because we just don't have a good tool to measure the outcome.

DR. LoCICERO: Dr. Olding.

DR. OLDING: If this was approved, this would be the only semi-permanent filler that we would have that has ever been suggested to last 21 months, so I think it's an important thing for us to consider before we agree that the labeling can say 21 months, particularly in view of the study measurement that we have, which is at least somewhat flawed.

I would agree that at six months I have no trouble with that whatsoever, but the number of responders steadily decreases over those 21 months. You have a patient who comes in and pays who-knows-what for a significant amount and you're anticipating, or they're anticipating, that it's going to last 21 months. They just paid you what is, to some of them, an arm and a leg, and I'm not comfortable telling my patients that, yeah, with the data that we have.

DR. LoCICERO: Ms. Timberlake.

MS. TIMBERLAKE: I just want to point out when it comes to patient cost, it's probably a little bit outside of the regulatory discussions that we're having, when it comes to labeling. It's an important issue. I think if it's covered in the labeling where they give full study results going out to the 21 months and showing the decrease and there's language in there that states something of the fact that individual results may vary and typically, we saw X at 21 months, with maybe the worst case and the best case seen in the study. That's the best at this point, though, it can do with the data presented today.

DR. ALAM: I think there might be some way to parse that in a way that that might meet both objectives, so saying we have six-month data indicating effectiveness for six months done in such-and-such a way and then there is indication from uncontrolled data that some of the results may persist for as long as 21 months. I think that puts it in sort of a way where there's no salesmanship, if you will, and there's no implied guarantee.

MS. TIMBERLAKE: I just also want to point out that FDA does review the marketing material if the product is approved. So they would look at all the marketing claims being made about the product to make sure it's within the data reviewed.

DR. OLDING: Let's disregard my comment about the cost, then, if you feel that's inappropriate.

This is, as you've said, a cosmetic procedure, and the expectation to delivery has to be very close, and I just want to be sure that our patients are not disappointed, number one, and number two, I have been on enough of these panels to recognize that if we say that they have an effect for 21 months, that's what will be advertised and that's what is out there, whether we talk about or feel that it's 6 months or 21 months or 3 years. So I'm just cautious about that.

DR. LoCICERO: Mr. Melkerson, concerning Question 4, the Panel feels that having another type of control would be useful, although it may introduce some of its own issues, but that a saline control or some other

control might be useful for new studies that do come up.

But the Panel seems to feel uniformly positive about the response to six months. Beyond that point, there is less unanimity in terms of the effectiveness of the product without further study.

Does this answer the FDA's questions concerning this issue?

MR. MELKERSON: I just wanted to make sure, when you're talking about future studies, you were talking about future studies looking at a shorter term, and in terms of suggestion for longer-term studies, you're still saying that open label is okay. Is that --

DR. LoCICERO: I think everybody agrees with that statement.

MR. MELKERSON: And I think the response is sufficient.

Thank you.

DR. NIELSEN: Question 5: The sponsor has proposed to evaluate the long-term safety of repeat treatment with Juvéderm Voluma XC using 12-month follow-up data from subjects enrolled in the premarket pivotal study. The proposed PAS plan addresses the postmarket concern identified by the FDA review team. However, FDA would like to receive input from the panel on the following: If FDA determines the premarket data demonstrate product safety and effectiveness, please discuss if there are additional concerns that should be evaluated in the postmarket setting.

DR. LoCICERO: Now we finally have an opportunity to talk about postmarket studies.

Any feelings concerning this?

Dr. Alam can begin.

DR. ALAM: I think a previous good point was brought up. I don't know the technical aspects of what can be in a postmarket study, so please correct me if I am speaking out of turn, but I would suspect this will be used off label for people older than 65, so it would be helpful to have data on that if that were appropriate to collect.

And I'm quite sure this will definitely be used off label in HIV patients since this is a common problem that is encountered by that patient population with regard to HIV lipodystrophy.

So those would be two populations I would suggest, and I would even suggest -- and this is, I think, not so strong -- possibly looking at some more data pertaining to non-Caucasian populations because while they were included, there were smaller numbers of them. And they did react a little bit differently in terms of both adverse events and in terms of effectiveness, even though given the small sample size, probably those differences didn't rise to significance.

DR. LoCICERO: So the Sponsor has suggested that they continue to study the patients who were enrolled in 002 for additional problems, and we're potentially proposing following new populations, some of which would be in the off-label thing.

Mr. Melkerson, you want to --

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MR. MELKERSON: I have a clarification comment.

Typically, post-approval studies are based on the indication that is approved for the product. If they want to look at those populations, typically they need their own datasets, which can come from various sources and various study designs, so if it's likely to be used off label, we would encourage the Sponsor to study those populations.

DR. LoCICERO: All right. So in that context, any further comments concerning the post-approval study, particularly as proposed by the Sponsor?

DR. McCAULEY: I think that post-approval studies, if I'm correct, are supposed to look at the performance of the product, not necessarily safety and efficacy. Is that true?

MR. MELKERSON: They look at both. Typically, it's long term.

DR. McCAULEY: Safety and efficacy?

MR. MELKERSON: It's basically to see if you are continuing having the same safety profile that you had at the primary endpoints.

DR. McCAULEY: I think that, looking at some of the subpopulations, I think -- subgroups -- it's very important, particularly in African-Americans, because they have thicker skin, they have thicker dermis, and they don't age with wrinkling. So I think that's very important to work out that subgroup and look at it.

DR. LoCICERO: And I think, at least in this particular trial, there

was a subpopulation of African-Americans, as opposed to many trials that we have seen before this Panel where there have been none. So at least in this particular case, there have been some recruited patients. So they at least have a group of patients they can begin with.

Dr. Chevray.

DR. CHEVRAY: Yeah, I just wanted to make a comment that I feel that a 12-month additional follow-up that's been proposed by the Sponsor is adequate for a product like Voluta that is non-permanent and, as we've seen, is likely to go away over the course of, say, two years.

DR. LoCICERO: Mr. Melkerson, concerning Question 5, the Panel feels that the proposed study by the Sponsor seems adequate, but with particular attention to the groups of patients with darker skin, particularly the African-American group, who may respond differently.

Does this address the FDA's concerns about Question 5?

MR. MELKERSON: I believe it does, but are there any other questions that the Panel thinks we should be looking at? That's part of this question. In other words, the Sponsor proposed something; is there anything else?

DR. LoCICERO: And that would be within the group of patients that they have studied. Is there other data that we can mine from this group?

MR. MELKERSON: What I heard you say was subsets of what they have studied and then there are subsets that they didn't study, but is

there anything else?

DR. ALAM: I think -- may I speak? It's Murad Alam.

I think I'm not sufficiently educated about FDA process, and it's probably my mistake to raise issues pertaining to populations that haven't already been studied, and I suspect if those other subpopulations are treated, I'm sure the company would, at some point, potentially collect data in a more standardized manner to address those issues. But I think within the context of the current application, that's not necessary.

Thank you.

DR. LoCICERO: And it may be possible that there will be further demand in some of these subgroups, such as those over 65, that might stimulate the Sponsor to study further.

Yes, Dr. Miller.

DR. MILLER: I wonder if there's a possibility for confusion between the two products where somebody might use the Voluta in a subcutaneous type of wrinkle-filling role instead of a volumizing role, if there's a need to look at what happens with that or -- I don't know.

DR. LoCICERO: I think we're going to address that in the next question. In terms of -- yes, Ms. Strong.

MS. STRONG: I was going to say earlier when we discussed the trauma infection related to the granulomas, would there be potential to gather data about people that may have -- someone mentioned acne or other

skin conditions or possibly even other traumas that happen to the skin around the injection areas to better understand whether there's potential correlation there?

DR. LoCICERO: I think that's an important point, particularly the eczematous or other conditions on the face would be important data to collect, and I don't think that's available yet.

Mr. Melkerson, does this clarify?

MR. MELKERSON: Yes, thank you.

DR. NIELSEN: So we're into the voting questions now.

DR. LoCICERO: I think we're at Question 6.

DR. NIELSEN: All right, so these are the voting questions.

DR. LoCICERO: Well, that went quick.

(Pause.)

DR. LoCICERO: We'd like to ask the Sponsor if they would like to make any summation comments at this point.

DR. AVELAR: On behalf of the Sponsor, I'd like to thank the FDA for their thorough review of the Voluta application, and for the Panel, for your time, thoughtful consideration, recommendations, and your comments.

Voluta met all primary and secondary effectiveness endpoints, and it's being pointed out that the safety profile was acceptable.

Importantly, patient satisfaction, by all measures, was high.

As we've heard today, one out of five patients in the United

States are being treated with injectable fillers to correct mid-face volume deficit even though they're not approved for this indication. We have an opportunity today to recommend a product that has been specifically developed, studied, and labeled for this indication.

Again, I'd like to thank the FDA and the Panel members for the review and your guidance.

Thank you.

DR. LoCICERO: Would the FDA like to make any additional summation comments at this time?

DR. NIELSEN: I'd first like to thank the Panel Chairman, Dr. LoCicero, and each of the Panel members for your participation in today's advisory panel meeting.

FDA brought Juvéderm Voluma XC to this advisory panel meeting because Allergan is seeking a first-of-a-kind mid-face indication. Effectiveness data presented today appears to support the Juvéderm Voluma XC product meeting the primary effectiveness and the secondary endpoint support effectiveness.

The safety data presented today showed that the common treatment site response elicited by Juvéderm Voluma XC continued in 20% of the subjects beyond 30 days becoming adverse events; 59% of the common treatment site responses were identified as moderate, and 19% were identified as severe.

Device- and injection-related adverse events were reported in 32.6% of the subjects with the majority of the adverse events resolving within 60 days. The clinical study reported three serious adverse events with delayed onset of six to seven months after treatment.

And, finally, the safety of Juvéderm Voluma XC may depend on subject age and injection volume.

And so we ask the Panel to consider these data in determining whether there is reasonable assurance of safety and effectiveness and whether the benefits of Juvéderm Voluma XC outweigh the risks.

Thank you.

DR. LoCICERO: Thank you.

Before we proceed to vote, I would like to ask Ms. Mattivi, our Consumer Representative; Ms. Timberlake, our Industry Representative; and Ms. Strong, our Patient Representative, if they have any additional comments.

Ms. Mattivi.

MS. MATTIVI: I just wanted to say thank you to the Panel and to the Sponsor. I felt the Sponsor did an excellent job with validating their tool and objectifying a very subjective area of study.

Thank you.

DR. LoCICERO: Ms. Timberlake.

MS. TIMBERLAKE: Yes, I just want to say, again, it's an

aesthetic indications for use, and the overall safety profile seems reasonable. I refer to light and laser where there are a lot more significant adverse events and dealing with a long-term bruise or nodularities. Definitely, the benefits outweigh the risks.

DR. LoCICERO: Ms. Strong.

MS. STRONG: I want to say thank you to the Panel and to the Sponsor, and I do commend the Sponsor for their thorough presentation and the facial measuring system, which I have written here, and what it does because I do think it is important, it's good to see. I have no concerns about the safety of this product and I guess no further comment.

Thank you.

DR. LoCICERO: Thank you.

We are now ready to vote on the Panel's recommendation to the FDA for this PMA. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit. Ms. Waterhouse will now read the three definitions to assist the premarket approval application voting process.

MS. WATERHOUSE: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device pre-market approval applications that are filed with the Agency. The

PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and reasonably be concluded by qualified experts that there is reasonable assurance of the safety and

effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

DR. LoCICERO: The Sponsor has proposed the following Indications for Use statement: Juvéderm Voluma XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face.

We will now proceed to the vote. Ms. Waterhouse will now go through the voting procedure.

MS. WATERHOUSE: Panel members, please use the buttons on your microphone to place your vote for the following three questions.

Question 1 reads as follows: Is there reasonable assurance that the Allergan Juvéderm Voluma XC is safe for use in patients who meet the criteria specified in the proposed indication?

Please vote now.

(Panel vote.)

MS. WATERHOUSE: Next question.

Question 2: Is there reasonable assurance that the Allergan Juvéderm Voluma XC is effective for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WATERHOUSE: And Question 3: Do the benefits of the Allergan Juvéderm Voluma XC for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

DR. LoCICERO: I don't think we're quite ready here. Hold on.

Okay, vote.

(Panel vote.)

MS. WATERHOUSE: Okay.

(Pause.)

MS. WATERHOUSE: Okay, on Question 1, the Panel voted a unanimous yes that the data shows reasonable assurance that the Allergan Juvéderm Voluma XC is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel also voted a unanimous yes that there is reasonable assurance that the Allergan Juvéderm Voluma XC is effective for use in patients who meet the criteria specified in the proposed indication.

And on Question 3, the Panel voted yes, that the benefits of the Allergan Juvéderm Voluma XC do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

I'll now ask each Panel member to discuss their votes for the record. Please state your name, how you voted, and why.

And nobody answered no, so that's it.

DR. LoCICERO: So let's begin with Dr. Burke.

DR. BURKE: I think certainly, because there are no permanent adverse reactions or deforming reactions, I think the safety is assured.

And I think that we've seen, by the criteria measured both from the examiner's point of view as well as the patient's point of view, that it was effective, and very excellently, for a longer term than similar injections.

And so I think that the benefits do outweigh the risks, and I think there is a need to have an FDA-approved material for this indication of volume enhancement since we have many FDA-approved things for wrinkle enhancement.

DR. LoCICERO: Thank you.

Dr. Alam.

DR. ALAM: I agree that this is a safe product as seen by the fact that there are very few adverse events beyond local site reactions, which seem to resolve usually very quickly. Sometimes it takes a few extra days, but they go away. It's well tolerated. Nothing seriously amiss happens, as far as we know.

With regard to effectiveness, based on the primary outcome measure, I think even in the worst-case scenario, it's clear that this is an effective treatment that does result in photographic evidence of diminution in mid-face atrophy.

And as the prior speaker noted, with regard to the approval

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process, this is the first injectable for the mid-face, and at present, there is none, so other products are being used off label. But it's good to have a product that is being used on label, and hopefully, with the postmarketing data, we can further get information pertaining to its utility and safety.

DR. LoCICERO: Dr. Ballman.

DR. BALLMAN: With respect to safety, the adverse events that were reported were not unexpected, and they were not disfiguring, and they could be reversible, so I felt that that was an adequate safety profile.

With respect to the efficacy, I felt that they met their primary endpoint, and also all the secondary endpoints were generally in the same direction, and some of them even stronger with respect from the patient evaluation, so I felt that they had established that. So given that, I felt that the risk/benefit ratio was good.

DR. LoCICERO: Dr. Miller.

DR. MILLER: I want to congratulate both the FDA and the Sponsor for trying to develop a nice objective way to measure effects on the mid-face, which we very badly need in this field. I'm convinced that this device is effective in augmenting the mid-face.

I think, as far as the safety issues, if this and the other Juvéderm product are not interchangeable, I think it needs to be clearly stated that -- you know, the different indications for those.

Also, I think it needs to be more clearly highlighted to people

how to recognize an event of an intravascular incidental injection and probably be recommended to have hyaluronidase available in the office for those kinds of events.

And then finally, as far as safety goes, some comment about if the skin barrier is compromised somehow, that there's an increased risk of infection with this device.

DR. LoCICERO: Dr. McCauley.

DR. McCAULEY: I pretty much agree with what everyone has said. I think the product is quite safe. I think there are a few bumps in the road, but as long as you know how to take care of them clinically, then that should not be a problem.

Efficacy, I think it's pretty efficacious. I think that six months is probably an adequate cutoff point until we get more data in terms of re-injections and how long this product will last under the skin.

And in terms of the depth of injection, I think you can't be exactly sure what the depth of injection is, but if that's part of the protocol and it's been done in the past, then it's safe.

DR. LoCICERO: Dr. Olding.

DR. OLDING: As far as the safety is concerned, I would agree that it is, by and large, a very safe product with just the caution about -- that I've discussed already, about long-term granulomas.

As far as the efficacy, I believe that they have demonstrated a

six-month endpoint that is certainly effective. I would have voted no if it was for 21 months, so six months, yes; 21 months, no. And as far as -- therefore, I voted yes on the third.

DR. LoCICERO: Dr. Chevray.

DR. CHEVRAY: Although there were some concerns about the validity and robustness of the mid-face volume deficit measuring tool, and the Panel had some concerns about the control group, my judgment was that Voluma XC is an effective product and device.

As far as the safety, we did not see evidence of any long-term permanent or disabling adverse effects, and we really didn't even see evidence of visible or disfiguring cosmetic adverse events, so I thought this was a safe product, and therefore, the risk/benefit ratio was favorable.

DR. LoCICERO: Thank you.

As the Chair, I do not have to vote unless there is a tie, but had I had an opportunity to vote, I would have voted yes on all three questions. For the narrow indications that have been suggested, this product seems to be safe, although there is a tiny group of patients who might have significant adverse events, and that the product is certainly effective based upon the measure that was validated by the Sponsor and approved by the FDA, and because of that, the risk/benefit ratio is in favor of the product.

At this time, I would like to thank all the Panel members for their deliberations and their careful evaluation of all the material that was

presented today and your time in coming here and deliberating with us.

I want to also thank the FDA for their hospitality, as well as their careful evaluation of the product and the data and presenting it to us in a way that we could understand.

And I want to thank the Sponsor for being responsive to our questions and presenting all of the information that we asked for, even though at times it seemed confusing and redundant.

So, in general, I think that we are very, very pleased by everyone's help in having us come to a final decision here.

Mr. Melkerson, we'd like to ask if you have any additional comments at this time?

MR. MELKERSON: Just a few parting comments.

I'd like to thank the Sponsor and the Panel for their time, the review team for their time and efforts, and have safe journeys home.

DR. LoCICERO: Thank you.

So the May 2nd, 2013 meeting of the General and Plastic Surgery Devices Panel is now adjourned. Thank you.

(Whereupon, at 4:10 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

May 2, 2013

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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