FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE MEETING

(MIDAC)

Wednesday, May 10, 2017

8:00 a.m. to 2:46 p.m.

FDA White Oak Campus

Building 31

10903 New Hampshire Avenue,

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Jennifer Shepherd, RPh

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

David B. Hackney, MD

Chief of Neuroradiology

Beth Israel Deaconess Medical Center

Boston, Massachusetts

Peter Herscovitch, MD, FACP, FRCPC, FSNMMI

Department Director

PET Department

National Institutes of Health

Rockville, Maryland

Paula M. Jacobs, PhD

Associate Director

Cancer Imaging Program

Division of Cancer Treatment and Diagnosis

National Cancer Institute

Bethesda, Maryland

Henry D. Royal, MD

(Chairperson)

Associate Director

Division of Nuclear Medicine

Mallinckrodt Institute of Radiology

St. Louis, Missouri

Alicia Y. Toledano, ScD

President

Biostatistics Consulting, LLC

Kensington, Maryland

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Richard A. Frank, MD, PhD

(Industry Representative)

Chief Medical Officer

Siemens Healthcare

Washington, District of Columbia

TEMPORARY MEMBERS (Voting)

Peggy Almgren, RN

(Patient Representative)

North Bay Endoscopy Center

St. Joseph's Hospital

Petaluma, California

Bonnie Arkus, RN

(Acting Consumer Representative)

Executive Director

Women's Heart Foundation

Trenton, New Jersey

Richard W. Byrne, MD

The Roger C. Bone MD Presidential Chair

Professor and Chairman

Department of Neurosurgery

Rush University Medical School

Chicago, Illinois

Mark R. Gilbert, MD

Senior Investigator and Deputy Director

Center for Cancer Research

National Cancer Institute

National Institutes of Health

Bethesda, Maryland

Donna R. Roberts, MD

Associate Professor

Department of Radiology and Radiological

Science

Medical University of South Carolina

Charleston, South Carolina

Lucia J. Zamorano, MD

Michigan Brain & Spine Surgery Center

Professor of Neurological Surgery

Oakland University William Beaumont

School of Medicine

Birmingham, Michigan

FDA PARTICIPANTS (Non-Voting)

Charles J. Ganley, MD

Director

Office of Drug Evaluation IV (ODE IV)

Office of New Drugs (OND), CDER, FDA

Libero Marzella, MD, PhD

Director

Division of Medical Imaging Products (DMIP)

ODE IV, OND, CDER, FDA

Nushin Todd, MD, PhD

Clinical Team Leader

DMIP, ODE IV, OND, CDER, FDA

Betsy Ballard, MD

Medical Officer

DMIP, ODE IV, OND, CDER, FDA

Anthony Mucci, PhD

Mathematical Statistician

Division of Biometrics I, Office of Biostatistics

Office of Translational Sciences, CDER, FDA

C O N T E N T S

AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
Henry Royal, MD	10
Conflict of Interest Statement	
Jennifer Shepherd, RPh	14
FDA Introductory Remarks	
Alex Gorovets, MD	18
Guest Speaker Presentation	
Cameron Brennan, MD	26
Clarifying Questions	51
Applicant Presentations	
Introduction	
Alan Ezrin, PhD	64
Visualization of Tumor During Glioma Surgery	
Constantinos Hadjipanayis, MD, PhD	69
Clinical Efficacy and Safety Results	
Walter Stummer, PhD, Dr med	84

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Benefit/Risk	
Constantinos Hadjipanayis, MD, PhD	119
Conclusion	
Alan Ezrin, PhD	125
Clarifying Questions	126
FDA Presentations	
FDA Clinical Review	
Betsy Ballard, MD	159
FDA Statistical Analysis	
Anthony Mucci, PhD	175
Clarifying Questions	188
Open Public Hearing	221
Questions to the Committee and Discussion	251
Adjournment	291

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ROYAL: Good morning. I'd like to first remind you to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Lauren Smith Dyer. If you are present, please stand. So she's in the back of the room in the corner there.

My name is Henry Royal. I am the chairperson of the Medical Imaging Advisory Committee, and I will be chairing this meeting. I will now call the meeting of the Medical Imaging Drug Advisory Committee to order.

We'll start by going around the table and introduce ourselves. Let's start on my right-hand side.

DR. HACKNEY: Hi. I'm David Hackney. I'm a neuroradiologist, chief of neuroradiology at Beth Israel Deaconess Medical Center in Boston.

DR. ROBERTS: I'm Donna Roberts. I'm a neuroradiologist at the Medical University of South Carolina.

MS. ALMGREN: I'm Peggy Almgren. I'm a nurse. I'm a patient advocate.

MS. ARKUS: Bonnie Arkus, consumer advocate.

DR. BYRNE: Rich Byrne. I'm a neurosurgeon at Rush Medical Center in Chicago.

DR. ZAMORANO: I'm Lucia Zamorano. I'm a neurosurgeon and a clinical professor of neurological surgery at William Beaumont, Oakland University in Michigan.

DR. FRANK: My name is Richard Frank. I'm chief medical officer of Siemens Healthineers. I'm a non-voting industry representative.

DR. ROYAL: Peter, why don't you go next? Sorry.

DR. TOLEDANO: You skipped me.

DR. ROYAL: Yeah, sorry.

DR. TOLEDANO: My name is Alicia Toledano. Good morning. I run a small biostatistics consulting company that focuses on clinical studies

of imaging devices and in vitro diagnostic devices.

DR. HERSCOVITCH: I'm Peter Herscovitch. I'm director of the positron emission tomography department at the NIH Clinical center in Bethesda, Maryland.

DR. GILBERT: I'm Mark Gilbert. I'm the branch chief of neurooncology at the NIH and senior investigator.

DR. MUCCI: Tony Mucci, statistics, FDA.

DR. BALLARD: Betsy Ballard, medical officer, FDA.

DR. TODD: Nushin Todd. Good morning. I'm clinical team leader at the FDA, Division of Medical Imaging Products.

DR. MARZELLA: I'm Louis Marzella. I'm the director of the Division of Medical Imaging Products. I'd like to welcome you to this meeting.

DR. GANLEY: I'm Charlie Ganley. I'm the director of the Office of Drug Evaluation IV.

DR. SHEPHERD: I'm Jennifer Shepherd. I'm the designated federal officer for the committee.

DR. ROYAL: For the topics such as those

being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal in today's meeting will be to have a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during lunch or breaks. Thank you.

Now, I will pass the meeting to Lieutenant Commander Jennifer Shepherd, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the Medical Imaging Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and

temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

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

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting,

expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves new drug application 208630 for five aminolevulinic acid hydrochloride powder for oral solutions submitted by NX Development Corporation for the proposed indication as an imaging agent to facilitate the real-time detection and visualization of malignant tissue during glioma surgery.

This is a particular matters meeting, during which specific matters related to NX Development Corporation's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

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

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. As a guest speaker, Dr. Cameron Brennan will not participate in committee deliberations nor will he vote.

We would like to remind members and temporary voting members that if the discussions involve any other product or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

DR. ROYAL: We will now proceed with the FDA's opening remarks from Dr. Alex Gorovets.

FDA Introductory Remarks - Alex Gorovets

DR. GOROVETS: Good morning. My name is Alex Gorovets. I'm a deputy director of the Division of Medical Imaging Products at the Center for Drugs. I would like to welcome this meeting's participants and including the applicant representatives, my FDA colleagues, our guest speaker, of course, and distinguished members of the advisory committee, and all the consultants who are assembled here today.

As mentioned already, as we all know, the application we are considering today and seeking advice on is the new drug application for 5-ALA, which is an optical agent for intraoperative use, to visualize malignant tissue during glioma surgery. The rationale is that drug is metabolized

by malignant tissue, makes such tissue fluorescence in certain light that's aiding the surgeons. So it sounds very simple.

Our guest speaker, Dr. Brennan, will go over the disease and its current treatments. We all know that malignant glioma is known to be a serious and deadly disease, and anything we can do from a public health perspective to advance its treatment, we'll consider quite important.

I will go briefly over some relevant regulatory background and then introduce the questions to the committee. Of note, to the imagers here, there's no image interpretation associated with the proposed use of 5-ALA.

This drug belongs to a pharmacologic class of optical imaging agents. As with any other imaging drug, we are guided in our regulatory approach by our guidances from 2004, specifically guidance part 2 on the clinical indications.

You will hear more about it, but for the purpose of this introduction, I would like to point to the main guiding concepts when it comes to

assessing efficacy of an imaging drug.

The proposed indication has to be shown or known to be clinically useful, and if so, then drug performance has to be assessed. That is how accurately it does what it claims to do.

Our drug regulations require that we approve a drug on the basis of statutory standards for safety and effectiveness. The regulations, and in fact U.S. law, require a demonstration of substantial evidence of effectiveness and define such evidence as evidence derived from adequate and well-controlled clinical investigations, usually more than one.

Specifically, in CFR 314.125, we are directed to refuse an approval if such evidence is lacking. And in 314.126, what represents adequate and well-controlled is actually defined.

This regulation specifically states that an adequate and well-controlled study uses a design that permits a valid comparison with a control. The relation goes on to actually list the types of controls such as placebo, dose comparison, no

treatment, active treatment, and states that such measures as randomization and blinding are recommended to minimize bias in the concurrent control design studies.

The same regulation also states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claim's effectiveness. However, it's very important to point out that the section of the regulations on the approval of applications also notes that while the approval of an application takes place after the drug meets the statutory standards that I just described, many drugs in their wide range of uses demand flexibility, and the FDA is required to exercise its scientific judgment to determine the kind and quantity of data needed for approval.

Back to the application, the application was granted a priority review, and prior to that, fast-track designation because we have agreed with the applicant that if approved, the drug would address an unmet medical need.

Back in 2013, the drug was granted an orphan designation, making it a candidate for orphan exclusivity if approved. It's a so-called 505(b)(2) application, because some of the clinical data the applicant believes we would have to rely on for approval does not belong to the applicant, meaning in this case they have published data as well. So for demonstrating efficacy, as you will see, the application relies on 3 clinical studies and 12 publications.

For the purpose of this NDA, the sponsor has gone back and selected a primary efficacy endpoint of biopsy level positive predictive value, defines a percentage of fluorescent biopsies that were confirmed as malignant on histopathology.

The proposed indication for the 5-ALA based on this endpoint is to facilitate the real-time detection and visualization of malignant tissue during glioma surgery, which we interpret as a single claim of visualization. So it's an imaging claim of visualization.

Now, due to the concerns related to whether

the primary efficacy data developed by the applicant for the purpose of this application is sufficiently controlled, as you will see, FDA reviewers have also looked at certain clinical outcomes for which controlled data have been available in the application. The examples of relevant clinical outcomes, with the extent of resection, survival, patient-reported outcomes, all these endpoints are more typical for therapeutic trials.

For diagnostic imaging drugs, we usually do not ask for clinical outcomes because of multiple confounders. However here, for proper assessment of drugs' risks and benefits, such an approach might be justified. We anticipate this will be an important theme for today's discussion, could some of the controlled clinical outcome data be supportive of what is the imaging visualization claim?

I'll go to the questions. I'll go through them pretty quickly so we can move on.

Question 1 will be of course on benefits and

discuss the efficacy outcomes used in this drug development program and the acceptability for substantiating the proposed claim.

In your discussion -- and this will be a discussion question -- please consider each of the following points. The applicant presented data demonstrating the intraoperative visualization of malignant tissue with a calculation of PPV.

Discuss the clinical significance of the provided PPD measurement and whether the provided data on malignant tissue visualization are sufficient for establishing efficacy of 5-ALA.

1B is discuss potential clinical importance of finding a non-fluorescent tissue being also positive for malignancy on histopathology.

1C is one of the efficacy outcomes used by the applicant is an improved completeness of resection defined in post-operative MRI. Please discuss the clinical importance of the "complete resection" and comment on the clinical meaningfulness of using post-operative MRI.

1D is assessing totality of evidence of

potential benefit of 5-ALA. Please comment on the clinical significance, if any, of the observed improvement in progression-free survival and lack of improvement in overall survival.

In your discussion, please comment on the following, whether either should be mentioned in the prescribing information if 5-ALA is approved for marketing in the U.S. and how the outcome of progression-free survival could relate to potential assessment of patient-reported outcomes, and what type of patient-reported outcomes would be relevant in this setting.

Now, question 2 also for discussion will be about risk. Please discuss the possible risk associated with increased resection, for example potential for increased neurological deficits or any other safety concerns you might have.

Finally, there will be a voting question. Do you recommend the approval of 5-ALA for the proposed indication as an imaging agent to facilitate the real-time detection and visualization of malignant tissue during glioma

surgery?

With that, I'm going to invite Dr. Brennan to give us a guest speaker presentation. Thank you.

DR. ROYAL: While Dr. Brennan is coming up to the podium, I realized there were two committee members who haven't introduced themselves yet. One is myself and the other is Paula Jacobs. I'm a nuclear medicine physician at Washington University in St. Louis.

Paula?

DR. JACOBS: I'm with the National Cancer Institute in the Cancer Imaging Program.

Guest Speaker Presentation - Cameron Brennan

DR. BRENNAN: First let me thank the audience today for the opportunity to address the panel members and guests and public and provide a background on neurosurgical removal of tumors.

I'm going to, in a brief review, go over some of the mechanics of tumor removal and how different classes of tumors affect how we take them out and what the benefits are. So I'll talk about

what kinds of tumors we operate on; how the surgeon maximizes extent of resection; what is the advantage of resection for infiltrating in malignant brain tumors; and what is the quality of data on extent of resection, a clinical outcome -- that's a large topic, but I'll just touch on it -- and some of the limitations for studies connecting extent of resection and outcomes.

I'm a surgeon in a cancer center, and I put up a pie chart, mocked up a pie chart, representing the kinds of patients that I operate on and treat. And rather than focusing on the pathologies of the tumors, I instead grouped them in a way by their physical characteristics.

So there are the benign, well-differentiated, and well-delineated tumors where our surgical control rates are excellent. Metastatic tumors represent a class of tumor where there is microscopic invasion, and they grow within the brain often. And our surgical control rates are still quite good, especially together with

adjuvant therapies. Then there are malignant and infiltrating tumors, where our surgical control rates in terms of cure are actually quite low, although surgery can offer many benefits.

Here's a cartoon of a brain with a dura layer over top. It looks like I won't be able to project any arrows.

I'll show an example of the first kind of tumor, the well-demarcated tumor. This would be typical for a meningioma. And it grows with a very sharp border with the edge of the brain. Here's an example from pathologic section. You can actually see the tumor as well as the space between it and the brain.

On an MRI, this is sort of a cartoon of a contrast MRI. You see the tumor lighting up or being bright with contrast material, and that's as a result of the vasculature carrying the small contrast molecules into the tumor, where they accumulate. And it's also because that same phenomenon doesn't happen in the brain, that the brain has a blood-brain barrier that prevents the

contrast material from passing in, so the tumor tends to light up whereas the brain does not.

Here's just an example of an MRI scan from a patient with meningioma.

When we remove a tumor like a meningioma, commonly we will shell it out because that's very safe, and then start to look at the intersection of the tumor with the brain. And because this is very well demarcated, we can dissect this and lift the shell away.

The limitation to complete resection is really involvement of the tumor in critical structures that we can't remove.

The second class of tumor is represented by a metastatic tumor and that is one that is growing within the brain and is locally invasive. And what I mean is, it has a sharp border in most cases, but if you look microscopically, tumor cells extend 2, 5 millimeters away. Here's an example of a pathologic section with the tumor on it. I don't know if it projects well, but I can highlight the tumor there.

This is a cartoon of the contrast MRI, and you'll see this is a little bit different. First, the tumor is dark in the center, and that's an area where there's little blood flow, often necrosis or dead tissue. It's not always the case, but it's common.

Around the outside, you see contrast enhancement, but it's blurry. And one of the reasons it's blurry is that the contrast that we're looking at, the enhancement, is not really marking the tumor. It's marking the blood vessels within the tumor and also feeding the tumor. The tumor cells are largely confined to the capsule, but also extend into adjacent parenchyma by a few millimeters.

So here's an example of a metastatic tumor. And the tumor itself is actually the gray inner object. And the blurry haze of contrast around it, that's actually enhancement in the blood vessels that are feeding the tumor. So again, the MRI is not necessarily marking the tumor, but is marking a secondary marker that we use to contrast the tumor.

So these are removed similarly to meningiomas with the understanding that, along the border, there can be microscopic disease left behind.

Fortunately, because the degree of invasion is very short, on the order of millimeters, that microscopic disease can later be treated with focal, other treatments, sometimes radiation. And the main limitation, again, is if the tumor is involved in critical structures, then we can't remove it.

Then the topic mainly for today is the third class of tumor, the infiltrating tumor. Now this is typified by glioblastoma, the most common tumor arising in adults in the brain from brain cells. So the cartoon that I've marked out has an outer edge here that is often highly vascular and looks very different than the adjacent brain. The inside is often necrotic and has poor vascularity.

But then the invasive component fades away, could be fading as tumor cells are migrating into adjacent brain. This transitional area of tumor

could be a centimeter or it could be 5 inches. The tumors can be relatively confined or they can cross even to the other side of the brain.

In this area, you'll transition from a histologic cut where you would see nearly a hundred percent tumor cells, and vascular architecture, and inflammatory cells, let's say, at the edge, to way, way out at the periphery, where you might see 1 tumor cell for every 100 normal brain cells.

So the surgeon has to consider -- as they're resecting, they have to consider what the transition area is and where they're going to stop. And this is typically done with our eyes and with looking at the color of the tissue, and what kinds of blood vessels do we see in it, and what is the texture. But we'll talk more about that.

Here's an example of a pathologic section, showing you a glioblastoma here. And you can see that it doesn't displace the brain. It actually replaces it. And it can have distant migration, shown by additional deposits.

An MRI schematic for GBM shows, again, a

necrotic center, poor access of agents in the blood to reach here, contrast-enhancing edge, which is also blurry for similar reasons. Only now, the blurriness of the contrast-enhancing edge extends over a wider territory. It's more heterogeneous because the tumor itself doesn't have a sharp border, an example of the glioblastoma with a dark center and bright rim, but also contrast enhancement that's wandering out.

There's another feature which is darkness on either side. That reflects on the MRI a loss of signal on our conventional contrast MR. And we think in those areas, or we know, that it's an area of the brain where there is both a high chance of tumor cells to hide and to actually change that MR signal, but also water that's forming edema or swelling that comes from the tumor.

So to remove these tumors, we can approach them with an internal debulking, but then we're left with the challenge of determining where to go next.

So the most obvious pathologically or

actually visually distinct tumor would be close to the sharp-enhancing edge, and sometimes we can see that visually; sometimes we can use MRI. Intraoperative MRI might be able to determine it. But there are also going to be boundaries where you're up against normal brain and where you're up against infiltrating tumor that may be hard to distinguish.

An intraoperative MRI taken at that time may show enhancement remaining, and of course that could be removed. But right along the edge, the MRI I've shown in white here, it's not because it's necessarily enhancing on the edge, but the edge is a difficult place for the MRI to resolve any residual. It has to do with how the magnetic field is affected by blood products and by air that may be in there.

So just right at the few millimeters around a cavity is an area where an intraoperative MRI scan is a little less sensitive.

So we talked about this dark signal around the tumor and how some of it could represent

infiltrative tumor and some of it can represent edema. So that's not very helpful in determining where to stop. So again, we may continue the resection into the non-enhancing tumor, but that decision is made based on a judgment of the visual appearance of the tumor, the texture, and then also what the surgical risk is and benefit to the patient.

Then there are non-enhancing versions of these tumors where there's an abnormality that's visible but less dramatic. You can see here -- actually, it's so vague, it's almost hard to see -- a pale and expanded area where tumor cells have really intercalated and displaced the brain. And on the MRI, these are non-enhancing. You'll see sometimes dark in this form of MRI, shown here for an example of non-enhancing tumor.

This dark area is where tumor is infiltrated. Here's a different version of FLAIR MRI, where we enhance -- or not enhance, we specifically turn that invaded and endenemous area white just to get it to stand out better. And we

can do a good resection for a tumor like this based on visual features like texture, but again, it's a challenge. And these tumors, both low- and high-grade gliomas, as I pointed out, can extend very broadly throughout the brain.

What do we use to maximize safe, surgical resection of tumors? Obviously, advanced neuroimaging has been critical, including anatomic imaging, metabolic imaging like PET, which can show us particular areas to target, as well as imaging of the function and functional anatomy of the brain in order to try to keep us safe, and those include functional MRI or additional anatomical views like diffusion tractography.

This is just a slide to represent there are other ways we can be safe. We can do operations with patients awake and to do cortical mapping around the area of a tumor in order to know where it is safe. Just to give you an idea of how hard it can be to see a tumor, this is where the tumor resides. It's discolored. If you're used to looking at brains, you can see it, but obviously it

can be subtle.

We keep track of where we are in the brain. Originally, this was done by frame-based navigation. The frame was screwed to the skull under local anesthesia. These are still used today for needles and catheters.

We've moved fortunately to adaptable frameless systems where a camera system can track objects in 3D, and we can recut the MRI scan dynamically as we're moving an instrument to show us where we are in the brain based on the pre-operative imaging.

We can mark out the boundary of a tumor. Like in this case, we can mark out contrast enhancement. Although again, when we look where the water and the invaded tumor are, they certainly extend far beyond that. We can use navigation to help us to resect a target in that sense by tracking our progress.

The limit of navigation is that as you're removing a tumor from the brain, there is shift of the brain and of the tumor cavity just because of

loss of buoyancy and the effects of gravity.

This is an image taken from an intraoperative MRI. An intraoperative MRI certainly gives us the ability to visualize that shift and get a new map for navigation so that if there's a little bit of tumor remaining, we can identify it.

This is one example of a lay-out for an MRI that's at our institution. The head is actually outside the main 5-gauss line of the magnetic field, so we can operate with conventional instruments there.

As an example of a case that's very well suited for additional visualization beyond what we can do with our eyes, this is an example of a patient with a biopsy, proven pilocytic astrocytoma.

Now, that's a benign tumor in the sense that it can be cured if we can remove it completely. But it is deeply located and it is an area of the brain that is quite heterogeneous with the nuclei and with the lining of the ventricle. So operating

down a very narrow channel, it can be difficult to determine if you've gotten the entire tumor out. A visualization aid like intraoperative MRI allows us to pick up the remaining tumor and target it for resection at that time.

I'm going to just diverge for a second and comment on intraoperative MRIs. I'm using it almost as a landmark for visualization, and the reason is simple. We use MRIs to diagnose tumors. We also use MRIs after surgery to see how much was removed.

We're trained to interpret MRIs to decide how much tumor we're going to take out based on those scans. So it is an imperfect visualization tool, but it serves as a very useful reference because of its universal adoption in pre- and post-tumor resection assessment.

When we installed the scanner in 2007, we used it for a variety of cases, but after a while, we've realized it was really most useful for these infiltrating tumors, high-grade and low-grade gliomas. It also has a very good use for benign

tumors like pituitary tumors where visualization is otherwise impaired.

The utility, we've really discussed. The limitations are, again, artifacts at the cavity edge after we've removed the tumor can limit sensitivity for tumor there. We cannot distinguish non-enhancing tumor from edema or swelling. And then there is not insignificant cost for a magnet that's well-underutilized when you compare it with a diagnostic MRI serving 1, 2, 3, 4 patients at best a day.

There has been continued and renewed interest in optical probes for imaging brain tumor. This was first introduced in 1948 with a description of fluorescein for a localization of brain tumors. That particular application really hasn't been well developed in part because an agent like fluorescein marks blood vessels and disrupted blood-brain barrier more than it does tumor in particular.

But there are many methods under investigation, including looking for intrinsic

optical signals from the tumor. And that can be fluorescence or Raman spectroscopy, tumor-specific markers like 5-aminolevulinic acid or chlorotoxin dye conjugates, and nanoparticles which can be tumor targeted and can be multi-modal in terms of visualization. So again, these are under investigation.

So given the cartoon models that I've shown you, it's just useful to look at what an optical tumor marker might have to do if it were to perform ideally and some things to think about when looking at investigational markers.

First, most markers are unable to pass through the blood-brain barrier. I don't want to speak generally, but that is generally true because most molecules can't pass through the blood-brain barrier, most drug molecules. They may pass through where the barrier is disrupted. So right around the edge, where we see contrast enhancement in this kind of tumor, this is an area where all sorts of agents can pass through.

An ideal marker, even though it may be

constrained to access the tumor through disruptive blood-brain barrier, we would want it to be reliable in labeling the tumor, both inside and outside. And in an ideal case give us a visual correlate of the tumor cell density. That's just what you would prefer. It would be an adjunct to making that same call by looking under white light with your eye.

But it's also important that the marker not extend beyond tumor and potentially lead the surgeon into normal areas of the brain. And actually, when you think of -- I saw positive predictive value come up in the introductory talk. When you think about it, that's a really key factor, both positive and negative.

False positives and false negatives are really quite important and potentially meaningful to the patient. False negatives, you would run the risk of leaving the tumor behind, although all of our methods using our eyes incorporate a false negative. We always do leave tumor behind in infiltrating gliomas.

False positives are more of a concern because they could potentially lead to surgical resection in any area that doesn't contain tumor or contains only a trivial amount. I won't go into it very much, but for non-enhancing tumors, the delivery of agents to the tumor is a concern, so for lower-grade gliomas.

So the goals for surgery for these tumors, for these infiltrating tumors, are really to establish the diagnosis, decrease tumor burden, relieve symptoms, improve neurologic function, extend duration and quality of life, and cure the patient.

I put them in order. This is in order of what we can hope to achieve. Duration, and quality of life, and curing the patient, we will fight for that as much as we can, but there's a limit to what surgery can do.

For glioblastoma, this was again the most common adult brain tumor, the balance of how patients do is affected by certain patient factors like age and how their neurologic and performance

status are, the tumor size -- tumor factors like size, location, histopathology, molecular markers. Those are things that are presented to us when the patient arrives. Then there were modifiable factors like extent of resection and adjuvant therapies.

This is an interesting comparison of how patients with glioblastoma who receive very similar therapy have done up to 1978 and then in the more modern era. And I'll draw your attention to the solid and red dashed lines.

There's been a clear improvement in survival from patients who have received surgery and radiation alone. Radiation really hasn't changed since the '70s. What has changed? Well, the advent of MRI, of operating microscope, of better neuroanesthesia, the advent of antibiotic usage.

This difference in survival for these patients is not really attributable to any one thing, but to advancements in multiple technologies. And actually, this kind of progress continues and also doesn't reflect other important

improvements in outcome like shorter length of stay for patients, less morbidity. Surgery has become since the '60s and '70s a much more tolerable and moderately more effective therapy, but not because of any one technology.

The literature on extent of resection and the benefit is, on the one hand, easy to understand. It's all retrospective, observational studies. And the quality of those studies vary, but the problems with the retrospective study don't really vary.

Then the main problem is bias. A patient who presents with a tumor in a very safe area of the brain or with a very small tumor might get a more aggressive resection. They may do better having nothing to do with the resection, but because they had a tumor in a safe area of the brain. Or a patient who is younger might be treated more aggressively just because of natural bias in the practitioners.

The standard of care, if you stopped any neurooncologist or neurosurgeon, for infiltrative

gliomas is maximal safe resection. And that's really the conclusion based on over half a century of studies on the management of these tumors. But if you try to really pin down what is the exact benefit of extent of resection, you're left with these retrospective studies because we can't randomize patients to receive a complete resection or not.

There has been in this over half a century numerous papers, and recently some really excellent reviews and summaries such as this one from 2016 by Hervey-Jumper and Mitch Berger.

In this, they take all of the studies they could find that fit the criteria for grade 3 and grade 4 of this glioblastoma and the grade just below anaplastic astrocytoma, and they separated the studies into non-volumetric and volumetric.

A volumetric study is one where usually a blinded radiologist scores the volume of tumor after surgery and before surgery so that the judgment of the surgeon isn't involved. Non-volumetric studies rely on non-volumetric

measures. It could be the surgeon makes a call about how much was removed or it's a classification of gross total removal or subtotal removal.

The volumetric studies are perhaps more systematic. In the review, they separated them between those that found a benefit of extent of research with outcome measures and those that found no benefit.

In summary, these were all retrospective. Most are level 3 evidence. I'd say essentially all are level 3 evidence except for 1 level 2B study; 23 studies in favor of an advantage for extent of resection and outcomes, 11 against. All volumetric studies show a benefit.

Again, it's very difficult to discern in the data how much you'd need to remove before patients benefit. And I will simply say, for the purpose of discussion, it is somewhere around 80 percent seems to be a consensus. Eighty percent of the contrast enhancement of a glioblastoma needs to be removed before you see a benefit in terms of an oncologic control of that tumor. There could be benefits to

lesser resection, benefits to the patient and in having them feel better, relieving symptoms, getting diagnosis.

There's one study that's the level 2B study that's worth showing because it's not really about whether there's a significant extent of resection benefit, but really is it substantial, is it useful to patients.

This is probably the best quality data we have in a single study due to the way that patients were accrued in the study. They were randomized to receive white light versus a fluorescence-guided resection. And the fluorescence-guided resection group got more gross total resections.

So when they went back and reanalyzed, they pooled. They looked at all the patients regardless of how surgery was done, who got gross total resections, and all those that had subtotal. In doing so, this dataset is enriched for variance in gross total versus non-gross total resection that was partially randomized. So in this case, we've got some signal that's partially randomized in

extent of resection.

What it showed is actually concordant with the rest of the observational data that between 4 to 6 months, a shift in mean overall survival, or median overall survival, seemed to track with gross total resection.

So what is that difference? Well, that difference is on the order of a difference between patients who are young and old in terms of how well they do on average. It's also comparable to the difference between patients who come in neurologically impaired or not. So it's a substantial difference.

There are many limitations to this particular study. I'll just point out these were a subset of patients who had glioblastomas specifically that the surgeon felt could be completely removed. So we're looking at a subset of patients.

I won't go into the literature for lower-grade tumors, but there, I think the evidence for resection is perhaps stronger in terms of benefit.

But I put the slide up just to show that, as with high-grade tumors, these are retrospective studies.

So what are the main limitations of studying intervention and outcomes in glioma? Gliomas are a heterogeneous group of tumors with variable prognostic and predictive features. They're rare and therefore it's difficult to accrue patients to clinical trials.

Many patients are treated outside of academic centers and are lost to study. And there are viable treatment courses, including timing and extent of surgery and adjuvant therapies. Progression is often associated with neurologic problems in patients, and this limits their participation in additional clinical trials.

In conclusion, infiltrating tumors such as gliomas present our greatest challenge for achieving maximal safe resection. The benefits of this are supported by level 3 evidence, and the quality of this evidence is unlikely to change in the next years.

Visual assessment of tumor under white light

during surgery remains the standard of care in the United States. Advancement in diagnostic, surgical, and medical technologies have improved patient outcomes incrementally and substantially over time. So I want to thank you.

(Applause.)

Clarifying Questions

DR. ROYAL: Thank you very much, Dr. Brennan.

Are there any clarifying questions for Dr. Brennan? Please remember to state your name for the record before you speak.

DR. JACOBS: I have a question. Paula Jacobs. You mentioned the use of intraoperative MRI. How common is that? How commonly available is that?

DR. BRENNAN: It is not common. If you look at all of the hospitals where patients with brain tumors are operated on, it's quite uncommon.

DR. JACOBS: So this would not normally be available to most patients?

DR. BRENNAN: That's correct.

DR. JACOBS: Thank you.

DR. ROYAL: Dr. Frank?

DR. FRANK: Yes, Richard Frank, industry rep. Two points of clarification if I may, please. One is, you mentioned that pre- and post-operative MRI are widely adopted. And you discussed intraoperative MRI, but you didn't characterize this in terms of how widely available that is.

Could you characterize that, please?

DR. BRENNAN: I'm not sure that I'm in a position to give numbers for access to intraoperative MRI, if that's the question. It is easy to say it's not widely available. It tends to be placed in academic centers or very busy, clinically busy, centers.

It's increasingly available. It has other applications outside of tumor resection. Those applications even involving surgeries elsewhere in the body, as they are established as important and effective, we may see it increasingly.

Right now, honestly, if you look at a patient who presents to an emergency room with a

newly diagnosed brain tumor and they're getting their diagnosis, quite often, that's where the patient will be operated on. And it is unlikely in that ER that the hospital associated would have an intraoperative MRI scanner.

DR. FRANK: Second question. You characterized the extent of resection above which there is clear benefit as being 80 percent of the contrast-enhanced area.

DR. BRENNAN: For a glioblastoma, yes.

DR. FRANK: Yes. Could you go one step further and say more is better? Is it simply a binary above and below 80 percent?

DR. BRENNAN: I see. Yes, yes. So that is an important point. More is clearly better. In fact, the early studies looked for a signal in terms of extent of resection at 97, 98, 99 percent. That's where you could most easily discern a benefit in terms of progression-free and overall survival. Then later on, the question became what is the minimum amount that we need to achieve before benefitting patients.

This question is really unresolved. So what 80 percent represents is that in studies now, volumetric studies where a specific analysis and study design are built to empower that kind of analysis, there is same quality level 3 evidence that you see a benefit down to 80 percent, maybe 70 percent, in high-grade tumors. In lower-grade tumors, there appears to be a benefit to even less of an extent of resection.

DR. FRANK: Thank you.

DR. ROYAL: Dr. Gilbert?

DR. GILBERT: Cameron, what would you say is the biggest challenge to achieving a gross total resection?

DR. BRENNAN: Well, we do use intraoperative MRI. And I wasn't trained on that, so I can say that our resections before and after -- the intraoperative scanner takes away much of the challenge of getting a gross total resection in a contrast-enhancing tumor. Now, that's different.

But we still are not infrequently surprised by contrast enhancement at the edges, where the

MRI, it simply doesn't give us an accurate read-out. I think, for all surgeons, the major limitation is simply where the tumor grows, that you may simply have to stop your resection for patient safety before you can get to a gross total resection. Those are the main challenges.

DR. HERSCOVITCH: Just to clarify a point of terminology, the terms "complete resection" or "gross total resection" are frequently used, but is it correct to say that that is really the immediate post-operative MRI evaluation, perhaps contrast enhancement, but almost certainly because of the infiltrative nature and the lack of blood-brain barrier breakdown surrounding the tumor?

That doesn't mean that you've resected all the tumor. You've just resected primarily the MRI radiographic portions of the tumor.

DR. BRENNAN: You are exactly right, and not just the MRI radiographic, but in these studies of high-grade tumors, it's the contrast-enhancing portion.

DR. HERSCOVITCH: Right. Yes.

DR. BRENNAN: So the infiltrated area may also be amenable to resection. That also may be important to resect, but when we study the effects of gross total resection or extent of resection, it's with regard to the contrast-enhancing area of the tumor.

For two reasons, one, it's measurable and we know what that is. We don't know what the infiltrative signal is. It could be water. It could be tumor. And number two, the area that's contrast enhancing happens to correspond with an area that's grossly abnormal to the eye.

DR. ROYAL: Dr. Hackney?

DR. HACKNEY: Sorry. I think we are running up against time, so I hope these are short. There are two questions I'll ask him about.

How often do you find that you have unexpected residual-enhancing tumor on your post-op MR? So that's tumor; you thought you got all the enhancing material out during surgery, but then the post-op MR shows some residual-enhancing tumor.

Then the second is, to the extent that this

new technique is intended to find tumor that you would not have planned to have resected based solely on the contrast enhancement properties, do you have an opinion about how well that lets you map onto whatever your guidelines for safe resection might have been; that is, your knowledge of the patient's anatomy, or your pre-op imaging, or your FMRI, or corticography to say, that looks like tumor, but it's not safe to take it out, or that looks like tumor, and I can go ahead and remove it?

DR. BRENNAN: You asked a short first question and a long second one. The first answer is, before using intraoperative MRI, just using eyes alone, if a patient came in with -- if we felt we achieved a gross total resection, I would say we were surprised on the post-operative scan at least a third of the time by some area. After the use of MRI, that's reduced perhaps to 10, 20 percent.

The second question is in part asking why do we continue resection outside of what's contrast enhancing. Well, I said it looks grossly abnormal

and that the adjacent area is also grossly abnormal, especially if it's in a safe area, and we know that the tumor will continue the resection. The stopping point, we really didn't spend much time on that. We talked about maximal resection. Maximal safe resection means your stopping point.

So we're trained to use our eyes to determine when we think the bulk of the tumor, the area that's 80, 90, 100 percent tumor cells, when that's starting to fade and transition into more normal brain, 50 percent tumor, 50 percent normal, even 10 percent tumor, 90 percent normal, and at the same time, to track where we are in the functional brain in order to avoid injury.

Whenever a new technology is brought in -- and that includes intraoperative MRI, but also optical markers -- surgeons need to be retrained so that they use that additional information, that new information, with the same skill and judgment of what's implied.

So I've been trained to know when a tumor is beginning to look like it infiltrates into normal

brain to the point that function could be injured, and it's an imperfect judgment. But we would need to be trained with intraoperative MRI or any other tool in the same way so that we know what our stopping spots are.

DR. ROYAL: Dr. Roberts?

DR. ROBERTS: Excuse me. You mentioned a 30 percent residual tumor before intraoperative MRI. Was that including with neuronavigation, which might be more widely available?

DR. BRENNAN: Yes, yes. And that's for patients where at the time of surgery, we thought we had gotten the entire -- I'm not saying that we achieved 70 percent gross total resections. I just mean, in the subset of patients where we thought at the end of surgery we must have gotten all the enhancement, I would say at least a third of the time, there'd be some area that was a surprise.

There are other neurosurgeons here today, and I think that's a question, not something that we necessarily score and have good numbers on, but something that maybe other surgeons can provide

their opinion on, too.

DR. ROBERTS: I guess I'm just to raise the question that intraoperative MRI is not widely available, but neuronavigation is more widely available. I'm wondering how that reduces the amount of residual tumor.

DR. BRENNAN: So when we are surprised by tumor, it's often along an edge. Because the brain shifts when the skull is opened, the resolution of neuronavigation, it varies case to case. But it can be, typically, during a large craniotomy, typically -- and it's been reported and measured. There's about a 2-centimeter shift in the brain compared to the pre-operative scan.

So wherever you touch the pointer, you're about 1 to 2 centimeters off, typically. And 1 to 2 centimeters is the width of a gyrus, one of the folds in the human brain. So we're not able to rely on navigation as well throughout the case. And the more tumor you remove, the shift becomes greater and greater.

DR. ROYAL: Dr. Zamorano, did you have a

question?

DR. ZAMORANO: Just maybe you can comment and clarify. In terms of the resection of tumors using intraoperative MRI, the goal is to remove the enhancing portion. So how many times do you run, on average, this intraoperative MRI sequence to remove the tumor?

This is just to make sure that some members of the panel understand that this intraoperative MRI is obviously not an online MRI, that it's just a sequence that has been -- or studies that have been done after certain intervals of time, but obviously this takes time by itself.

So how many times on average do you run this?

DR. BRENNAN: The average would be 1.1 times. So about 9 cases out of 10, it's just one intraoperative MRI assessment, and then occasionally, we'll do a second one. That's just our practice.

Each time we get a scan, we have to interrupt surgery. The patient has to be covered

and draped. They have to be brought into the magnet, then the room cleared. All the electricity goes off except for the critical equipment. The scan is taken over about 20 minutes, and then the patient is brought back out, reregistered in the navigation system, redraped.

So it can be an interruption of a half an hour or 40 minutes. It also pays back in terms of speed of surgery when you know what you're taking out is enhancing tumor. It gives the surgeon an idea, a map that we have another 1 centimeter to go in this direction, then 2 centimeters, and we can move through that space more quickly.

So not all of the time taking the scan is lost time to the patient. We actually gain some back by having that updated map. I hope that answers the question.

DR. ZAMORANO: So just to clarify, in most cases, when you say it's just one time, it means that you run an intraoperative MRI and you assess that you did a resection as you had planned.

So the intraoperative MRI really didn't add

any good picture, or this means that every time you run one MRI again, and then you do another resection?

DR. BRENNAN: Yes. So I would say in about half the cases -- just to give you an idea of our experience with it, about half the cases at the time we think we're done with our white-light assessment, the MRI confirms it. In about half the cases, we find additional tumor and then target it for resection.

But if what we see -- so the patient's brought back out. We have a map. We have new neuronavigation. We can point directly at the area of residual tumor. We go in and look at it. If what I see with my eyes matches the MRI -- if I see the tumor, and I see that it has edges that if I get to it, that is removed, then we don't get another scan just to document it. It's a balance of patient interest and the additional time needed.

DR. ZAMORANO: Thank you.

DR. ROYAL: If there are no other clarifying questions, we can proceed to the sponsor's

presentation.

Applicant Presentation - Alan Ezrin

DR. EZRIN: Good morning, advisory committee members, FDA representatives, and attendees. My name is Alan Ezrin. I'm the founder and president of NX Development Corporation, and we are the sponsor of the new drug application for 5-aminolevulinic acid, also known as 5-ALA.

This slide summarizes the proposed indication for 5-ALA. 5-ALA is an imaging agent to facilitate real-time detection and visualization of malignant tissue during glioma surgery.

For patients with primary brain tumor, maximal, safe surgical resection is the first step in the standard of care worldwide followed by treatment with radiation and chemotherapy.

The reality you will hear today is that this is a lethal disease. Brain tumors cannot be completely removed, and the extent of resection is a primary driver of survival. Despite progress in the field, the majority of surgical cases failed to achieve complete resection, and these tumors

returned within 6 to 12 months, leading to the death of the patients.

Malignant glioma is a rare and serious life-threatening tumor. Unlike other solid tumors, it is highly infiltrative and difficult to delineate the margins.

The image on the left is a solid tumor and cell culture illustrating the tentacle-like invasiveness of this tumor. The tumor is very difficult to approach based upon the heterogeneity of the border. Clean margins are virtually impossible to achieve.

The goal is to maximize resection and preserve vital brain regions. The problem is that the surgeons can only remove what they see. Fluorescent-guided surgery using 5-aminolevulinicacide, as shown on the right, is the topic of today's discussion. It provides the neurosurgeons with real-time visualization for accurate and precise information on the location and the extent of the tumor.

5-ALA is orally administered to patients

three hours prior to surgery. It is a prodrug, preferentially taken up by glioma tumor cells and metabolized in all cells to its fluorescent metabolite, protoporphyrin IX.

Protoporphyrin IX is in everyone's body as an intermediate and hemoglobin synthesis. Protoporphyrin IX selectively accumulates visible levels in tumor cells and not in normal cells.

Upon illumination with filtered white light from the microscope, which we will refer to as blue light, the protoporphyrin IX can clearly be seen by the surgeon using the standard microscope. Fluorescence indicates malignancy with a high predictive accuracy, allowing surgeons to make critical real-time decisions.

The clinical development of 5-ALA for brain tumor visualization was conducted by our colleagues at Photonamic and Medac who conducted six clinical trials in Germany to support the registration in Europe in 2007. We have partnered with this team, who are here with us today, to bring 5-ALA to the neurosurgeons in the United States.

Currently, 5-ALA, known as Gliolan, is available to neurosurgeons for the visualization of glioma in 40 countries worldwide. To date, the worldwide experience is over 58,000 exposures.

NX Development Corporation holds the commercial license in the United States. 5-ALA received orphan drug designation in 2013 and a priority review in 2017. We have participated in several meetings with the agency pertaining to the use of the European clinical data in its totality along with peer-reviewed publications demonstrating the safety and the efficacy of 5-ALA. These data were submitted in December of 2016 in our new drug application and are summarized in your briefing document.

As you will hear today, 5-ALA is not curative, but a vital imaging tool that allows surgeons to achieve the procedural goal, to safely minimize the amount of tumor left behind. As a cancer survivor, I have a personal motivation to bring this imaging tool to neurosurgeons in the United States.

During our presentation, we will review the highlights of the development program and the benefits that are associated with 5-ALA. I am pleased to be joined by my European and U.S. colleagues who have trained over 400 of their colleagues in the use of 5-ALA. They will be presenting with me today.

Dr. Hadjipanayis is the director of neurosurgical oncology at Mount Sinai Hospital in New York City. He holds an investigator-sponsored IND and has used 5-ALA in over 100 surgical cases. Dr. Hadjipanayis will be speaking next about the standard of care in glioma surgery and the use of 5-ALA in clinical practice.

We are also joined by Professor Stummer from the University of Munster, who is the chair of the department of neurosurgery. Professor Stummer and his research teams brought 5-ALA from the experimental setting to the clinical use and approval in the rest of the world. He was the principal investigator for the clinical studies conducted to support the European approval, which

are contained in our new drug application and serve as the centerpiece for our submission.

Dr. Stummer has published over 43 peer-reviewed publications on the use of 5-ALA to visualize glioma tissue. Dr. Stummer will be presenting the clinical efficacy and safety data.

Dr. Hadjipanayis will return to summarize the benefit and the risk profile of 5-ALA. I will then offer some concluding thoughts.

At this time, I'd like to introduce Dr. Constantinos Hadjipanayis.

Applicant Presentation - Constantinos Hadjipanayis

DR. HADJIPANAYIS: Good morning. My name is Constantinos Hadjipanayis, and I am professor and chair of neurosurgery at Mount Sinai Beth Israel and director of neurosurgical oncology for the Mount Sinai Health System. I am a consultant medical advisor for NX Development Corporation. I also have a financial interest in 5-ALA.

In order to set the context for visualization of tumor during glioma surgery, I will first briefly cover glioma incidents,

prognosis, presentation, as well as standard of care, and the goal of safe, maximal extent of resection.

I will discuss the limitations of current available tools for glioma surgery and what the current unmet need is. Finally, I will lead us through 5-ALA and fluorescence-guided surgery for real-time visualization of tumor.

As you heard, gliomas are brain tumors which occur in 14,000 to 30,000 patients a year. The majority of these are malignant gliomas which are World Health Organization grade 3 and 4 high-grade tumors. The most common of these are glioblastoma, also known as GBM.

These are deadly tumors. Patients can live anywhere from 15 to 36 months despite any type of therapy including surgery, radiation therapy, and chemotherapy. Gliomas are devastating tumors with no cure. They rarely metastasize. Most commonly after surgery, they grow back in the area where the tumor originated. Even in the case of low-grade gliomas, almost all transform to high-grade

malignant gliomas with time.

Most patients with gliomas present with headaches and/or a new onset seizure. Depending on the location of the tumor, their speech, motor function, or eyesight may be impaired. Typically, patients are seen in the emergency room, where they undergo evaluation, have a CAT scan and an MRI scan.

In malignant glioma patients, gadolinium contrast enhancement is seen on MRI. The tumor often causes swelling with the surrounding brain and shift of the brain depending on the size of the tumor. With imaging, however, we really do not know what glioma grade the patient has at presentation. Despite poor prognosis, we treat glioma patients as aggressively and safely as we can with surgery, radiation, and chemotherapy.

Our current approach most commonly includes surgery for histopathologic diagnosis confirmation in maximal safe resection of the tumor. When we cannot surgically resect the tumor due to the deep midline location of the tumor or involvement of

multiple sites in the brain, we perform a stereotactic needle biopsy for tissue diagnosis.

High-grade glioma patients go on to chemo and radiation. As you heard, this standard of care and treatment includes fractionated radiotherapy with concurrent adjuvant chemotherapy. Patients with recurrent high-grade gliomas can undergo repeat surgery, re-radiation, or chemotherapy with bevacizumab.

Low-grade glioma patients can undergo observation after maximal surgical resection, or adjuvant radiotherapy, and/or chemotherapy if they have a subtotal removal of the tumor. Almost all these tumors recur and transform to malignant gliomas.

The global consensus for surgical management of gliomas is maximal safe resection. All our major societies and institutes have adopted this consensus, including our parent bodies in neurosurgery in this country, the NIH, the NCI, as well as our European colleagues and other cooperative groups around the world.

As surgeons, we rely on preoperative MRI to see the tumor which we will attempt to resect. Here's an example of what that looks like.

Here's an MRI of a malignant glioma tumor. In the pre-op image on the left, we see a contrast-enhancing area with a central necrosis present. Our goal is to perform a maximal extent of resection and completely resect the contrast-enhancing portion of the tumor.

As you can see in the center and right post-op images, the tumor has been removed in a maximal fashion as no residual contrast enhancement is present except for remaining blood products.

Gliomas are highly invasive and infiltrative tumors. At the margin, glioma tumors are difficult to visualize, and as a result, a maximal extent of resection is very challenging. Both of these figures illustrate how the malignant cells reside centimeters away from the tumor mass and it's therefore impossible to resect all of the cells. Because of this, all the recurrences of tumors are within 2 centimeters of the original tumor in the

majority of cases.

When I operate on these types of tumors, the first question the family asked me in the surgical waiting area is, "Doctor, did you get all the tumor out?" And my response is that I took out all I could see and safely remove. We do know that the more tumor we safely take out, the better the outcome the patient will have.

As reported in a number of publications, the amount of tumor resected in both high- and low-grade tumors is associated with patient benefit. The published literature on thousands of patients support the correlation between maximal extent of resection and better overall survival of the patients.

We know this associated increase in overall survival is also incremental with the volume of tumor contrast enhancement removed. Furthermore, greater extent of resection also permits better efficacy of chemoradiation treatments.

It is important to note that the majority of patients do not have a maximal extent of resection

due to the lack of tumor visualization and tumor location adjacent to critical tracts in the brain.

When we assess glioma patients as neurosurgeons, we want to understand and localize where the tumor resides. We want to understand the relationship of the tumor with the surrounding important tracts in the brain that involve the motor function, speech, vision, and sensation.

This image represents a pre-operative MRI scan with imaging called diffusion tensor imaging that lets us look at those tracts. The blue areas show motor fibers adjacent to the rim enhancement of the tumor.

Our most important function with surgery is not only maximal extent of resection, but preservation of neurologic function. The last thing we want to do is take the tumor out and tell our patient and family, "I took out all the tumor I could see, but this left you paralyzed on one side." This outcome would certainly highlight how we did not understand the relationship between tumor motor fibers, between the motor fibers in

tumor during surgery.

In the operating room, we do have tools available for glioma surgery. The most widely used technology is called neuronavigation, and that allows us to localize the tumor. However, this is based on a pre-operative MRI scan and is not real time.

Not only when we take the bone off, but when we resect the tumor, there is shift of the brain that then renders the neuronavigation system inaccurate for the course of surgery, as you heard before.

In the operating room, we also have some techniques to find those important pathways I discussed. We perform intraoperative electrophysiologic mapping. We also perform awake brain surgery to understand where those speech pathways are for glioma tumors that involve or are close to speech centers. However, even with these tools, we still have difficulties visualizing the tumor well.

We have some tools that are available in

some centers that can help us determine if we have resected all the tumor we can see. One of those you heard is intraoperative MRI, which is not available at most U.S. centers.

IMRI, intraoperative MRI, frequently involves transport of patients to another room in many occasions, interruption of the flow of surgery, and delay of surgery. Intraoperative ultrasound can be used for real-time image guidance. However, the resolution is low and can be difficult to interpret during surgery.

So as neurosurgeons, we have major challenges with glioma removal. When we have safely resected all of the tumor we can see, we really don't know how much tumor is left due to its infiltrative and invasive biology. We can't precisely understand the relationship of the tumor with the surrounding functional tracts or pathways present, which questions how we can safely remove gliomas.

How can we localize the tumor in real time? Even intraoperative MRI will only give you a second

MRI scan during surgery that is a snapshot in time. It will not continuously give you an MRI image in real time while you operate.

The brain shift with brain surgery is a major problem that makes our most commonly used neuronavigation technology unreliable, and unfortunately, some of the technologies and tools are simply not available at all centers.

What do we need as surgeons for optimal glioma resection? We definitely need a tool that provides us real-time visualization of malignant tumor. We need to delineate the tumor tissue from normal tissue. I need to be confident that what I resect is in fact malignant tumor tissue. We need something that's unambiguous and in high resolution for intraoperative imaging that would permit resection of a glioma tumor in real time to actually guide surgery and safely preserve important surrounding tracts.

I want to perform my surgery not relying on technology based on a pre-operative MRI scan that doesn't take into effect the brain shift during

brain surgery. My goal is to achieve a maximal extent of resection in a safe manner.

Here on the left is the glioma resection cavity of one of my patients, shown by the arrow. At the tumor margin, it is difficult to delineate infiltrating tumor from normal brain, as you heard.

Now, this is a high-grade malignant glioma. We thought we performed a maximal extent of resection based on our neuronavigation. According to the green crosshairs in the corresponding neuronavigation figure on the right, we're outside the area of contrast enhancement. It is likely inaccurate due to the brain shift from removing the tumor. We did not have an intraoperative MRI at my center where this patient was operated on. We thought we were done with the tumor resection, but not really confident we were.

As you can see in the resection cavity, there does not appear to be tumor tissue present. The underlying white tissue appeared normal. In fact, we were not done with the surgery. Once we turned on the blue light, the resection cavity lit

up with fluorescence. There was fluorescent tissue present that delineated residual malignant tumor tissue that I would not have seen had the patient not received the 5-ALA.

The tumor fluorescence guided my surgery in real time, and I was able to resect the residual tumor. Also, I can actually see the surrounding brain with the blue light. I'm not operating in the dark here.

5-ALA is taken up by malignant glioma tumor cells and then metabolized within the tumor cells to its fluorescent form, protoporphyrin IX. Protoporphyrin IX selectively accumulates in malignant tumor cells.

5-ALA at 20 milligrams per kilogram is orally administered 3 hours prior to anesthesia. Malignant glioma tumor tissue will fluoresce at least 8 hours after administration. 5-ALA does not fluoresce on its own.

This illustration shows a patient in surgery and our use of the standard conventional microscope we neurosurgeons use every day in operating rooms

throughout the world. The microscope in this illustration has the filter modification that emits blue light, which you can see by the blue arrow. The 410-nanometer wave length of blue light excites the protoporphyrin IX metabolite of 5-ALA, which then emits a red light.

5-ALA is safe. Some patients can have skin sensitivity when exposed to bright light after 5-ALA dosing within 24 hours. 5-ALA is metabolized by the liver and patients can have a transient elevation in their liver function tests.

Here's a video of the same patient in the photos I've shown you. Let's look at this in real time. This is the same resection cavity in the pictures displayed earlier. We've dried up the resection cavity with a cotton pad, and we're looking through the standard microscope with white light. We cannot visualize tumor in the resection bed.

We're about to switch over to the blue light to visualize any residual tumor present. We quickly switch over by the push of a button, and

we're operating now under blue light. You can still visualize the surrounding brain, but immediately within view is the red fluorescent tissue that's very obvious.

There's no difficulty visualizing this. I know with high certainty that this represents tumor, and I can confidently remove this tissue, keeping in mind the surrounding important tracts we discussed. The fluorescent tissue delineates the tumor from the surrounding normal brain. It's guiding my surgical resection of the residual tumor in real time.

There are many desirable characteristics of 5-ALA. It is convenient to use and administered just once orally prior to surgery. Patients with new or recurrent glioma tumors can also be administered 5-ALA.

We can use our existing microscope with a blue light filter for this. 5-ALA is an adjunct to our standard surgery and operative tools. And most importantly, it provides real-time visualization of malignant tissue previously unseen with white

light, so I can perform a maximal extent of resection without disrupting the overall flow of surgery.

In summary, let's all remember that gliomas are deadly. Maximal safe extent of resection is our surgical goal and is our standard-of-care treatment for this lethal cancer. Almost all glioma patients go onto other adjuvant therapies after surgery. We know that the ability to localize the tumor from the surrounding critical functional tracts in the brain is essential to safe tumor removal and preservation of neurologic function.

Glioma tumor margins are difficult to visualize under standard microscopic white light. Presently, we don't have localization tools that provide continuous real-time tumor visualization for guidance of our surgery.

There is no question that better glioma visualization will allow us to provide better surgical care for our patients and achieve a safe maximal extent of resection. Improved surgery will

also impact downstream therapies our glioma patients will likely need.

I would like to now introduce Dr. Walter Stummer, who will present the clinical efficacy and safety results.

Applicant Presentation - Walter Stummer

DR. STUMMER: Thank you Dr. Hadjipanayis.

My name is Walter Stummer, and I was the principal investigator for most of the 5-ALA multicenter clinical trials. I'm also a consultant for NXDC and Photonamic.

I'm grateful for the opportunity to speak about the data support and the use of 5-ALA for visualization of malignant brain tumors during surgery as an adjunct to conventional microsurgery. This agent helps us to detect additional tumor tissue and to decide what to resect without the uncertainties involved with traditional tools.

Proving the benefit of 5-ALA-induced fluorescence is not without challenge because seeing the tumor is only a small part of what the neuro surgeons are doing during treatment of

malignant glioma patients. State-of-the-art resection, multi-disciplinary decisions, and adjuvant treatments are other parts.

First, I would like to summarize the data supporting the use of 5-ALA. I will review some of the endpoints we have used to scientifically demonstrate the usefulness and benefit of this method.

Neurosurgeons understand the advantages for surgery, however, we do have to show that this method is useful for patients. In this context, it should be kept in mind that 5-ALA is a tool for surgeons to facilitate surgery, and surgery is the therapy.

I will present the pivotal studies for the EU approval, studies 3, 28, and 30, which provide clinical data on the use of 5-ALA. I will then review the endpoints described in the NDA, which focus on visualization and predictive accuracy and discuss the usefulness and limitations.

Finally, we will show how predictive accuracy fluorescence translates into clinical

usefulness, helping the surgeon see more under the surgical microscope and that this correlates at least to tumor contrast enhancement on the MRI. Neurooncologists and neurosurgeons agree that resecting this part of the tumor is the aim of surgery for malignant gliomas.

In addition to our clinical trial data, the evidence to be presented here today, and which is outlined in the briefing book, encompasses scientific literature and global postmarketing data collected after approval of ALA in Europe in 2007.

Together, this includes 418 patients for efficacy and 527 patients for safety in our clinical trials, 377 patients for efficacy, and more than 2,000 patients for safety from the literature, and more than 58,000 patients from global postmarketing data.

First, I will review efficacy. Here is a summary of the clinical development program, which supported the registration in Europe and other countries and now supports the NDA. Study 20 was a bioavailability trial, study 8 a trial for dose

finding and safety, and study 32 was a large trial with 243 patients, which focused specifically on safety.

Three studies, studies 3, 28, and 30, generated both efficacy and safety data. Study 3 was a large randomized trial in newly diagnosed malignant gliomas randomized between conventional microsurgery or conventional microsurgery and ALA fluorescence.

The main intention of study 28 was to determine whether tissue fluorescence in normally appearing brain truly predicted tumor tissue, to what tumor cell density tumor could be visualized, and how its fluorescence is identified using neuronavigation related to contrast enhancement on the early post-operative MRI.

Study 30 was in recurrent gliomas, and it aimed at determining the positive predictive value in marginal tissue after resection of identifiable tumor under white light.

Due to its role in the approval process in Europe, I would first like to introduce study 3.

This was a randomized group-sequential, controlled, multicenter phase 3 study of the impact of using 5-ALA for tumor visualization during resection. For bias reduction, central neuroradiological and neuropathological assessment was blinded to treatment.

Patients who met the entry criteria, which included suspected malignant glioma, were randomized to either be operated on using standard white light microsurgery, the control group, or the 5-ALA arm where 5-ALA-induced tumor fluorescence was added to conventional white light microsurgery.

The study had two primary study endpoints, extent of resection of contrast-enhancing tumor and the rate of progression-free survival at 6 months. Secondary endpoints included safety, volume of residual tumor, and overall survival.

415 patients were randomized in a 1 to 1 ratio with stratification by age, Karnofsky Performance Score, eloquent tumor location, and study site.

We specified a power of 80 percent with an

experiment-wise type 1 error of 0.05. We did prespecify an interim analysis after 270 patients in the full analysis set to allow for early termination for futility. Multiple endpoints and the interim analysis were adjusted for appropriately.

Patients were enrolled based on imaging alone. For this reason, we did anticipate that a number of patients would not meet the entry criteria such as patients with incorrect histology, for example abscess or metastasis, or showing no contrast enhancement.

We pre-defined these patients as not qualifying for the assessment of efficacy, that is, for section rates and PFS. If these patients had been administered ALA, however, they were allocated to the safety analysis set. Importantly, blinded neuropathologists and neuroradiologists identified those patients not qualifying for the efficacy analysis.

As the table shows, 415 patients originally enrolled in the study. A total of 66 patients did

not qualify for the full analysis set, which consisted of 349 patients. Importantly, the characteristics of patients not qualifying for the full analysis set were well balanced between study arms.

Accordingly, the full analysis set was well balanced regarding our known prognostic factors indicated in the slide, namely for age, Karnofsky Performance Score, and the location of the tumor regarding eloquent regions of the brain, and grade 3 or grade 4 histology.

This study met the first of its primary endpoints. When the surgeon used 5-ALA for fluorescence visualization during resection, the percentage of patients with a complete resection of contrast-enhancing tumor was nearly doubled to 64 percent compared to the 38 percent in the white-light control group. Without the use of 5-ALA, roughly two-thirds of the patients had incomplete resections under white light alone.

This improvement of resection was obvious for all subgroups. This forest plot shows the

different patient subgroups in study 3 by age, KPS, and eloquent location of the tumor. The benefit of using 5-ALA for fluorescence-guided surgery was seen in all subgroups as indicated by the homogeneity of the odds ratios.

The second primary endpoint was also met in study 3. Six months' progression-free survival rate based only on post-operative MRI as assessed by blinded neuroradiological raters was found to be significantly greater in patients in the 5-ALA arm of the study, being increased from 11 to 20.5 percent, with use of 5-ALA compared to resection under white light alone.

As previously shown for resection rates, the homogeneity of the odds ratios between study arms and subgroups was also maintained, showing the putative benefit of using 5-ALA for fluorescent-guided surgery to be similar for all subgroups, regardless of age, KPS, or tumor location.

As an additional analysis, we also generated Kaplan-Meier curves from our data on progression-free survival. These curves also show a

significant difference in favor of patients randomized to the 5-ALA arm by the log rank test.

However, it must be remembered that these curves are primarily driven by the degree of resection rather than by patients having received the study drug. Therefore, to analyze the impact of resection on PFS alone, we restratified patients based only on extent of resection.

Using the data from the NDA, this graph was developed to show progression-free survival of all patients restratified into patients with complete versus incomplete resections of contrast-enhancing tumor independent of study group.

The Kaplan-Meier curves indicate that the primary driver of progression-free survival was extent of resection of contrast-enhancing tumor rather than the study group drug. In the further analysis, we now stratified these groups with complete and incomplete resection by their original study allocation, thus generating four curves.

The blue curve on the right is for those patients with complete resections in the 5-ALA arm,

the green curve for patients with complete resections in the white-light-only arm. These curves are about the same. Furthermore, no real differences were observed for patients with incomplete resections using 5-ALA, the red curve, and white light only, the brown curve.

Please note that the number of patients in the 5-ALA fluorescent light group that achieved the complete resection was 112. That is almost double the number of only 65 white-light patients that received a complete resection. For incomplete resections, this was just the opposite.

This means that using 5-ALA, surgeons are effectively moving a large subgroup of patients from the group of patients with worse prognosis to the group of patients with a better prognosis regarding progression-free survival.

On the other hand, overall survival, as depicted in the left graph, was not found to be different in the full analysis set. This was possibly due to the many interventions these patients are later exposed to, and again the fact

that not study group allocation was driving outcome, but extent of resection.

On the right graph, we are showing a similar exploratory analysis with substratification as we presented for progression-free survival with survival showing similar effects.

During the approval process in the EU, EMA specifically asked for exploratory analysis that underlined the clinical significance of improved PFS for patients in the ALA arm. We therefore looked at the time point and frequency of repeat surgery, which we considered interventions triggered by observing progression in these patients.

This cumulative incident graph shows the incidence of repeat surgery on the Y-axis and months on the X-axis. The incidence of repeat surgery was significantly lower for patients whose resections were performed using 5-ALA fluorescent light versus white light only.

Having demonstrated the patient benefits in study 3, I would like to review the endpoints used

in this NDA for supporting the claim of improved visualization and clinical usefulness of 5-ALA.

Specifically, we asked the essential question, when tissue fluorescence is used in 5-ALA, does it truly show malignant tumor? The positive predictive value, or PPV, plays an important role in this analysis. PPV is defined as a number of biopsies that show tumor over all fluorescent tissue biopsies.

This value was determined for studies 3, 28, and 30. With study 28, we additionally assessed to what cell density can infiltrating tumor in the brain be made visible using 5-ALA. Further, we evaluated whether the additional use of 5-ALA fluorescence allowed the surgeon to visualize more tumor than with the use of white light alone and how fluorescence relates to enhancement on the MRI.

As I mentioned, we collected multiple biopsies in our studies 3, 28, and 30 for assessing the positive predictive value of fluorescence on a biopsy-based and on a patient-based level.

In the randomized study 3, these biopsies

were not the primary or secondary study aim. In study 28, biopsies were correlated with post-operative imaging using neuronavigation. In study 30, biopsies were obtained from fluorescent tissue after the surgeon had removed the bulk of the tumor under white light.

The NPV, or negative predictive value, which is the number of fluorescence negative tumor samples over all fluorescence negative samples, was also calculated from the histological data for all our studies.

In study 3, one biopsy each was taken from solid tumor, marginal tumor, and normal tissue if feasible under blue light for assessing fluorescence. Again, these biopsies were not supervised nor correlated with location, for example, by neuronavigation. Thus, because we did not know from where investigators took the biopsies, we could not correlate the histologies to post-operative MRI.

There was also no specific indication of whether biopsy sites were first identified on the

fluorescence or on the white light. Nevertheless, the PPV for strong fluorescence was 98.7 percent, for weak fluorescence 97.0, and for any fluorescence, 97.8 percent.

Let us now turn to study 28. This study was a prospective, multicenter trial in 33 patients who had malignant gliomas. The study was designed to correlate visual fluorescence with histology, with samples taken at the margins after bulk tumor resection as indicated in the top right illustration. Our goal was to assess the cell density visualized by fluorescence.

The study was also designed to correlate residual fluorescing tissue left unresected for safety reasons with an enhancement on post-operative MRI. We could locate these regions using neuronavigation. Thus, the study also intended to determine whether fluorescence was more sensitive for detecting residual-enhancing tumor than MRI.

In study 28, surgeons resected to the tumor margins, exposing fluorescing tissue. Under normal circumstances, we are able to distinguish two

qualities of fluorescence as shown on the right.

The center of the tumor is usually surrounded by a region of reddish strong fluorescence. This region is surrounded by a region of weaker, more pink fluorescence. In this study, surgeons were asked to perform multiple biopsies in the area of strong and weak fluorescence.

Fluorescence was first measured objectively using spectrometry. This measurement was supervised by a physicist. If feasible, samples were also collected from the region immediately adjacent to the pink fluorescence, and also, if feasible, distant to the fluorescing tumor.

Samples were assessed by central neuropathologists blinded to the location of the biopsy. Residual areas of fluorescence that were not amenable for resection were located using neuronavigation. This tool was used to record the anatomic location in the brain. These data were later compared to early post-operative MRI by an independent neuroradiologist.

This video shows an interoperative cavity in which suction is applied to the tissue surrounding gross tumor. To the neurosurgeon, this tissue looks quite normal under white light. Under blue light, this region shows clear fluorescence, indicating infiltrating tumor.

The video contains a small measuring scale placed in the cavity to show how high the resolution of the method is at about 1 millimeter. As mentioned, we utilized this resolution in study 28 for obtaining samples from fluorescing tissue at the margin, tissue new to the tumor, and tissue at a distance from the tumor.

This slide summarizes some of the data from study 28. The graph shows tissue tumor cell densities on the Y-axis, stratified by fluorescence type on the X-axis, either strong or weak, or no fluorescence; the latter stratified by where the samples were taken, either right next to the fluorescing margin, which is the bright blue box, or at a distance, which is the dark blue box.

The bars indicate median cell density. The

box is the 25th and 75th percentile range, the whiskers, the entire range.

Median tumor cell biopsies and biopsies with red fluorescence was 90 percent; with pink fluorescence, slightly more than 10 percent. In negative biopsies taken immediately next to the fluorescing tumor, the distribution of cell densities was significantly lower, indicating an about 1-log reduction in cell density when resecting fluorescent tumor.

Neurosurgeons and neurooncologists will agree that this log tumor cell removal should be considered a benefit. As expected, even at a distance from the tumor, cell density was not null.

From the biopsies in study 28, we also determined the PPV of fluorescence for indicating tumor. The biopsy-based PPV in the study was 100 percent for strong fluorescence, 92.2 percent for weak fluorescence, and 96.2 percent from a total of 185 biopsies.

In study 30, on the other hand, the approach was different and simpler. This study was a

multicentric prospective study in 40 patients with recurrent malignant glioma.

In this study, surgeons were asked to perform tumor resections under white light. At the margins of the tumor, they first identified normally and abnormally appearing tissue under white light. They then switched to blue light, collecting biopsies from these areas if they fluoresced.

In this study, we found PPV in biopsies with strong fluorescence of 98.2 percent, and biopsies with weak fluorescence of 95.3 percent, and overall of 96.6 percent. Thus, the PPV in recurrences was comparable to newly diagnosed malignant glioma.

This slide summarizes the PPVs found in fluorescing tissue at the margins of brain tumors. It was comparable and high in all three studies in regions with strong fluorescence at almost 100 percent and slightly lower in regions with pink fluorescence at the margin. This information is invaluable to the surgeon when deciding which tissues he or she should resect.

Our findings are in line with the literature, as many other study groups, with minor exceptions, all determined a PPV of 95 to 100 percent with the exception of a study with only 46 biopsies obtained in 23 patients by Panciani, et al., who found a PPV of 89 percent.

On the other hand, we also calculated the negative predictive value, or NPV, from our biopsies. The NPV is defined as the number of fluorescents negative to tumor biopsies over all fluorescence-negative samples.

In three studies, the biopsy-based estimate of NPV were between 18.8 and 24.1 percent, indicating that many biopsies taken from non-fluorescing margins in our studies still harbor tumor cells.

Regarding NPV, the literature gives a much larger variability from between 20 to a size 90 percent as summarized in this graph. This invariably raises the question on how these disparities can best be explained.

Recall that, since tumor cells in malignant

gliomas spread diffusely throughout the brain, it is not possible to completely resect all tumor cells. This is also not necessary since the aim of resection is the resection of enhancing tumor. Even with a complete resection of enhancing tumor, residual tumor cells will often be detectable. Therefore, although fluorescence denotes malignancy, the opposite conclusion is not completely true, namely that lack of fluorescence shows normal brain.

The negative predictive value now depends very strongly on where the sample is taken. If samples are taken close to the cross-tumor, as indicated in the illustration, values will be low. If samples were taken remotely from the tumor, these values will be much higher.

In addition, the frequently-used diagnostic measures, sensitivity and specificity, are also affected by true and false negative samples, and these will also depend on where the samples are collected.

Nevertheless, looking at the biopsy-based

diagnostic measures from our pivotal studies, despite their limitations, we find acceptable values in studies 28 and 3 with surgery for newly-diagnosed malignant gliomas. In study 30, specificity appears exceptionally low with a value of 20 percent. Study 30, however, is a study on recurrent malignant glioma.

The recurrent malignant gliomas, as we clinicians well know, are highly infiltrative beyond the region of contrast enhancement, invading a much larger volume of adjacent brain. With these tumors, it is virtually impossible to find correctly non-fluorescing negative marginal tissue, which does not reveal low-level infiltration of tumor cells.

In study 30, only 3 truly negative biopsies were found and only 16 samples from non-fluorescing tissue were collected. This accounts for the low calculated specificity in the recurrent study. Note, the PPV in that study was still high.

This table is from the FDA briefing document. In general, it confirms high

specificities and sensitivities using 5-ALA despite the obvious limitations regarding these methods. Please note that because specificities depend strongly on the truly negative samples and the collection of such samples depends on the distance from the main tumor mass, these have a considerable variability.

Keeping this endpoint in mind, we demonstrate efficacy in the NDA by showing the predictive accuracy of fluorescence and highlighting to the surgeon tumor tissue infiltrating the brain. This accuracy is based on the positive predictive value or PPV.

In the absence of a meaningful interpretation of NPV, we are also looking at other indicators of clinical usefulness in the NDA, that is, helping surgeons to find tumor tissue using fluorescence that might otherwise have been overlooked using a surgical microscope with conventional white-light surgery. Studies 28 and 30 also addressed the second question.

In study 28, our multicenter prospective

study, surgeons were asked to resect all fluorescing tumor that was safely amenable to resection. Residual areas of fluorescence were then mapped and related to brain anatomy using neuronavigation. Neuroradiological raters blinded to the fluorescence findings determined whether contrast-enhancing tumor was present at these sites, recorded by navigation.

Among the 33 patients, 42 regions with residual fluorescence were identified and assessed by navigation. This is the blue bar on the left. In only 14 regions, that is, 33 percent, as represented by the gray bar on the left, these regions were visible on MRI as contrast-enhancing tumor.

Importantly, 32 of these regions, as indicated by the blue bar on the right, appeared inconspicuous under white light but contained tumor on MRI and pathologically.

The conclusion is that fluorescence shows more malignant tissue than white light and that tumor may not be visible as enhancing tissue on the

MRI.

In study 30, the multicenter prospective study on recurrent malignant gliomas, tumor was first resected to its white-light borders. Tissue was then determined as abnormal or not under white light. Surgeons then switched to blue light and collected biopsies from fluorescing residual tissue, which they investigated by neuropathology.

Despite these tissues looking normal under white light in 157 locations, fluorescent tumor was found in 146 of 157 biopsies with a high PPV of 93 percent. Thus, this study confirmed that fluorescence will help identify tumor not visible as such to the surgeon under white light and will help guide resections.

To conclude, our studies show that 5-ALA-induced fluorescence enhances structural visualization of malignant tumor intraoperatively, which aids surgery, thus underlining utility. This visualization is highly accurate, as measured by the PPV of fluorescence. The usefulness of this is the ability to see additional malignant tumor.

Furthermore, fluorescence encompasses at least the enhancing tumor.

By meeting both our primary endpoints in the randomized controlled trial, we demonstrate that 5-ALA fluorescence-guided surgery leads to a significant increase in percentage of patients with maximal extent of resection and improve progression-free survival at six months. Furthermore, post hoc analysis demonstrates a reduced need for subsequent surgeries.

A wealth of peer-reviewed literature are consistent with the clinical trial data. Overall, the data demonstrate that 5-ALA-induced fluorescence provides more informative visualization than white light alone that can guide resections and benefit both the surgeon and the patient.

This concludes the review of the efficacy data. I will now summarize the safety data.

In this section, I would like to review the data we have generated throughout our clinical studies, data that is available from the

literature, as well as postmarketing surveillance data from the EU.

Assessing the safety of 5-ALA fluorescence-guided surgery involves considerations of risks in three areas: those related to the drug, those related to surgery, and those related to surgical decisions based on the enhanced visualization.

Risks related to surgery depend on patient factors such as the underlying disease, tumor location, steroid pre-treatment, comorbidities, and a population with a median age of 63 years, and patient selection. Also, brain surgery for malignant gliomas carries significant risks and depends much on the performance and experience of the surgeon.

Finally, there may be risks related to resecting more tissue due to enhanced visualization. However, an experienced surgeon will rely on structural information and knowledge of eloquent areas of the brain and will take all factors in consideration when deciding on the amount of tissue to safely resect.

In this section, I will present the information that is available on safety using 5-ALA, keeping the different risks in mind. The safety population is based on data derived from clinical studies with a total of 527 patients, data from published clinical studies was a total of about 2,000 patients, and the postmarketing surveillance data from the EU with about 58,000 recorded patients so far.

Patients in five studies comprised the full safety population. Each patient received 20 milligrams per kilogram body weight 5-ALA. Please note that study 3 included a control group that did not receive study drug and study 8 included patients who received lower doses. Therefore, these patients are not included in the full safety population.

For analysis of adverse events, we use the following definitions. Treatment-emergent adverse events, or TEAEs, were defined as AEs that start or worsen during or after administration of 5-ALA and were reported as mild, moderate, severe, life-

threatening, or fatal.

TEAEs were also categorized as short-, mid-, or long-term events, that is to say, short-term within one week of surgery, mid-term after one week but within 6 weeks of surgery, and long-term after 6 weeks of surgery.

Any event deemed by the investigator to be certainly, probably, or possibly related to 5-ALA was coded as related to 5-ALA. In addition, if the relationship was unknown or data was missing, the event was coded as related.

Before presenting the data in detail, I would like to again emphasize that malignant glioma patients are a seriously ill population with a variety of neurological impairments and receive a variety of adjuvant therapies.

Glioma is universally fatal and the population has a high median age. As noted previously, resection surgery itself is associated with frequent intra- and post-operative risks and side effects.

Please note that because 5-ALA is

metabolized and eliminated within about 24 hours, and side effects of surgery are recorded immediately after surgery, with the exception of infections, mid- and long-term events are expected to be influenced by tumor progression or side effects of adjuvant therapy such as radio or chemotherapy.

Of the 527 patients in the full safety population, 317 of them experienced a total of 802 events. Of these, 23 events were rated by the investigator to be drug related. In addition, 133 patients experienced a serious adverse events and 25 patients experienced events that resulted in death. These data are not stratified by the time point of occurrence.

It is notable that event rates for 5-ALA-treated patients were comparable to patients in the control group in the randomized clinical study, study 3.

The most frequently reported events were nervous system disorders, which mostly occurred within one week of surgery. This was the case in

about 30 percent of patients. The neurological deficits that occurred during 1 to 6 weeks of surgery in patients who received 5-ALA were indistinguishable from patients who did not receive the study drug. Again, with these neurological events, it has to be kept in mind that they're likely due to either the disease and/or the surgery.

Here's a summary of the most frequently reported nervous system events. These were unlikely drug related. Eleven patients experienced events that were considered drug related in the first week after surgery. Short-term events that were not explained by the procedure were hypotension and abnormal liver function tests. Events unrelated to surgery were also reported in the mid- to long-term period. These were reported as drug related or with an unknown relationship to the drug.

This is a summary of patients that experience events considered drug related within the first 6 weeks after surgery, which are

exceptionally low.

Serious adverse events occurred in 133 patients; 13.1 percent of these were reported within one week after surgery. Again, the most common serious adverse events were nervous system disorders, which were expected with patients undergoing glioma surgery.

In 10 percent of patients, serious events occurred in the time period between 1 and 6 weeks after surgery, and in 7.3 percent of these patients, serious events occurred more than 6 weeks after surgery.

Serious adverse events reported in the first week after surgery are likely a result of the procedure itself rather than the 5-ALA. 9.3 percent of patients experienced the serious adverse events that are listed in this summary.

As I noted previously, neurological events were indistinguishable between patients who received 5-ALA and those in the control group. In this slide, we show the data from the randomized study, study 3. Neurological sequalae were closely

scrutinized and compared to the cohort of patients that had had conventional surgery without 5-ALA.

This table summarizes all neurological severe adverse events, but also shows all grade 3 and 4 neurological events as extracted from the common toxicity criteria lists. Overall, the total number of neurological adverse events when comparing control and 5-ALA patients were the same.

Those adverse events qualifying as grade 3 and 4 according to the CTC list were equally frequent in both study arms. The number of neurological adverse events qualifying as severe were also similar in both study arms. From this study, no obvious concerns were raised regarding additional resections using 5-ALA.

For assessing safety, we also used an instrument which is traditionally used for assessment of the degree of neurological function in stroke patients, the NIH Stroke Score. This is a very sensitive instrument which captures even minor changes, for instance in the strength of an arm or a leg.

This slide shows the statistic for the NIH Stroke Score. Forty-eight hours after surgery, 26 percent of patients in the 5-ALA arm had an increase in NIH Stroke Score compared to 14.5 percent in the control group of 1 point or more. This difference decreased over time and was no longer apparent at 3 months.

These differences in neurological function captured by the NIH Stroke Scale did not translate into a difference in general function. General function was assessed by the Karnofsky Performance Scale, first at 6 weeks after surgery, at 3 months, and 6 months after surgery.

We did not see any significant difference between the study groups. At 6 months, patients in the 5-ALA group tended to have less deterioration based on tumor progression than those in the control group.

In the clinical studies, a total of 284 deaths occurred over 18 months. Twenty-five patients died in this period as a result of a treatment-emergent adverse event. No deaths

reported were considered related to the administration of the drug.

As I explained, malignant glioma is a fatal disease. Consequently, such deaths were found during the observation period in the safety cohorts. No clinically significant pattern of change was detected that was associated with 5-ALA in extensive laboratory evaluations with the exception of transient increases in transaminases and gamma-GT. There have been no reports regarding ECG abnormalities such as QT prolongation or rhythm disturbances.

This table shows the transient increases in transaminases and gamma-GT. We did see a higher incidence of grade 3 and 4 toxicities than in the white-light control arm. These subsequently were covered with further follow-up.

Numerically, the levels were only significantly increased at 24 hours. The increases were not considered a clinically relevant indicator of liver dysfunction.

To summarize, regarding the clinical study

data, only a small fraction of the events were considered to be related to the drug. Nervous system disorders were the most frequent emergent adverse and serious adverse events that were reported. These were most likely due to disease and/or surgery.

There were a few events that led to death, but none of them were related to the 5-ALA. We observed no clinically meaningful patterns of change in the laboratory values with the exception of the transaminases or ECG measures.

In addition to the data from the clinical studies, we conducted a comprehensive literature search regarding side effects of 5-ALA. We were able to identify 29 studies that provided data on the safety of 5-ALA. These 29 studies included around 2,000 patients. No specific patterns of new adverse events or reports of 5-ALA-associated mortality were found.

Postmarketing surveillance data collected since 2007 were last reported in 2015. 58,000 patients dosed with 5-ALA did not reveal any

pattern or side effect that might be related to the use of 5-ALA for brain tumor surgery.

In conclusion, there is an extensive safety database available for 5-ALA from clinical studies, from published literature, and from postmarketing experience. 5-ALA has a well-established safety profile, and the adverse events that have been reported are most often a result of the procedure or the underlying disease and only rarely related to the drug. Neurological disorders were the most frequently reported adverse events and consistent with those seen with standard resection surgery.

This concludes my presentation of safety. I would now like to ask Dr. Hadjipanayis back to the podium.

Applicant Presentation - Constantinos Hadjipanayis

DR. HADJIPANAYIS: As a neurosurgeon using 5-ALA in our center in the U.S., I would like to summarize the benefits and risks of 5-aminolevulinic acid for visualization during glioma removal.

We seek to better visualize malignant tumor

tissue during glioma surgery. The standard of care in the U.S. and the rest of the world is maximal tumor resection. Maximal resection of the contrast-enhancing portion of the tumor is associated with better outcomes in glioma patients.

We acknowledge that data is mainly retrospective. Outcomes in these patients are, however, difficult to measure due to the fact that these patients move on to other therapies once their tumor occurs.

We know that all patients have residual glioma left after surgery due to the infiltrative biology of these tumors and the challenge of identifying tumor at the margin. We also cannot accurately delineate tumor from normal brain in real time during surgery.

As you heard from Dr. Stummer, with 5-ALA fluorescence-guided surgery in multiple clinical studies, we can visualize malignant tumor with high accuracy as demonstrated by a positive predictive value of approximately 95 percent.

This has been confirmed by a number of other

published studies. Accurately visualize a malignant tumor that could not be seen with standard white light can also permit more malignant tumor resection.

In the phase 3 study, 64 percent of patients had a maximal extent of resection with 5-ALA compared to 38 percent of patients who had surgery without 5-ALA. Maximal extent of resection was associated with greater progression-free survival in patients who underwent 5-ALA fluorescence-guided surgery. The PFS at 6 months was 35.2 percent compared to the control group of 21.8 percent. 5-ALA fluorescence-guided surgery provides real patient benefit.

I would like to summarize the benefits of 5-ALA in fluorescence-guided surgery. This is a safe agent. Over 58,000 patients have been dosed with 5-ALA with no deaths directly attributed to the agent and minimal toxicity associated with the agent.

5-ALA is a high-resolution intraoperative visualization tool that provides unambiguous

delineation of malignant tissue. The more malignant tumor tissue that can be visualized, the more tumor that can be resected safely. 5-ALA fluorescence-guided surgery is compatible with our current standard, surgical microscope, it is orally administered prior to surgery, and it does not disrupt the flow of surgery.

There are no worries of losing accuracy of localization due to brain shift with 5-ALA fluorescence-guided surgery. And based on the randomized phase 3 study, glioma patients have greater maximal extent of resection, progression-free survival at 6 months, and fewer repeat surgeries.

I would like to summarize the perceived risks with 5-ALA in fluorescence-guided surgery. After 5-ALA administration, additional malignant tumor can be visualized, which the neurosurgeon could not see under white light.

Glioma surgery carries inherent risks to patients, including potential neurologic deficits due to the important tracts that surround tumors.

Neurological deficits can occur with or without 5-ALA. The neurosurgeon makes the decision as to whether additional tumor tissue can be safely removed or not utilizing their judgment, experience, and intraoperative tools we discussed. Not all patients can have a maximal extent of resection due to the critical tracts adjacent to tumors.

Temporary skin photosensitivity can occur within 24 hours of 5-ALA dosing. Patients are kept in subdued lighting to prevent any skin sensitivity immediately after surgery. Patients can have transient LFT elevation. Those patients have normalization of their LFTs after dosing.

5-ALA fluorescence-guided surgery is a new paradigm in neurosurgery. Based on our experience with the drug in Europe, we have created the 5-ALA Medicines Management Program. This program consists of three parts: an educational program to instruct neurosurgeons of the proper use of 5-ALA fluorescence-guided surgery. This programs limits 5-ALA use to neurosurgeons who have been certified

after instruction. Recertification is also proposed every two years. 5-ALA will be shipped and dispensed from hospital pharmacies where surgeons have been certified.

In summary, we have an unmet medical need for improved visualization of malignant glioma tissue during surgical resection, where our goal is to perform a safe, maximal extent of resection in these patients with this deadly disease.

5-ALA provides real-time visualization of the tumor tissue that guides the surgery. It provides structural delineation of the tumor from the normal surrounding brain that contains critical important motor, speech, or sensory pathways so they can be preserved.

It provides the neurosurgeon unquestionable visualization of tumor tissue that he or she would not have seen without the drug so that more tumor can be confidently removed.

There is clear patient benefit that has been demonstrated in a phase 3 randomized study where glioma patients given 5-ALA had better PFS at

6 months, almost double maximal extent of resection, and fewer repeat surgeries. 5-ALA is safe for our patients, as seen in multiple clinical trials and published studies worldwide.

Let us all remember that gliomas are a universally fatal cancer. Patients with high-grade malignant gliomas have a median survival less than 2 years despite all therapies, and low-grade gliomas eventually transform to high-grade gliomas with time. We need technologies that will help our patients.

Based on the totality of the evidence, including data from the clinical studies, published literature, and global postmarketing experience, as well as my experience in over 100 patients, 5-ALA has a clear benefit, which greatly outweighs any risks.

I would like to invite Dr. Ezrin back to the podium to conclude our presentation.

Application Presentation - Alan Ezrin

DR. EZRIN: This concludes our presentation. We have demonstrated the efficacy and safety of 5-

ALA in the data presented today and submitted in the new drug application, including the clinical studies, the worldwide literature, and the postmarketing experience.

5-ALA is not a therapy. It's not a curative agent. 5-ALA is a much needed real-time imaging tool providing accurate visualization to support safe surgical resection of gliomas. We thank you for your careful consideration in our discussion today.

Clarifying Questions

DR. ROYAL: Thank you to all the presenters.

Are there any clarifying questions for the sponsor? What I would suggest is if you put your name tag up, I'll be able to tell who has questions. Dr. Todd?

DR. TODD: Thank you very much, Dr. Royal. I'd like to start by thanking our speakers for excellent presentations. Thank you very much.

I'm just seeking clarification on the very last slide and Dr. Ezrin's earlier presentation about the proposed indication.

The proposed indication for 5-ALA is for real-time detection and visualization of malignant tissue during glioma surgery. I'm just seeking clarification in the sense that the approved indication in Europe for which the data that was presented here is for grade 3 and 4 gliomas, for high-grade. And the data that was presented for today that was submitted focused on high-grade gliomas.

Certainly, I know that we don't know the grade until at the time of surgery. But the approved indication in Europe is for grade 3 and 4 based on the efficacy data, and it's the same efficacy data that was provided today.

So I just wanted to get a clarification on that disconnect between glioma in general, the lower grade, that I don't believe there was any presentation on the efficacy of 5-ALA on the lower grade.

DR. EZRIN: Dr. Todd, your observations are correct. We are seeking as broad of a label as the data will support, and we're utilizing

visualization of malignant tissue during glioma surgery. We are using the same data, the efficacy studies, study 3, 28, and 30, which supported the EU label, which does have the grade 3, grade 4 delineation to it.

Our difficulty is in understanding what is a grade 2 or a lower grade. And the literature is complete with numerous examples that we don't understand the malignant nature of what one is defining as a grade 2.

Perhaps during the Q&A, we can get into a further discussion around the data that has been seen that supports malignant presence in grade 2, which could make this appropriate. It's a subject for discussion. Thank you.

DR. ROYAL: Dr. Mucci?

DR. MUCCI: I have two technical questions. On the slide, I think it was CR-3, for PFS, there were two numbers, I think 35 percent and 21 percent down there, 6-month. On the earlier slides, the CEs, I thought there was a 22 percent versus 11 percent.

DR. STUMMER: Walter Stummer. Yes, you are absolutely correct in your observation. These numbers were in fact derived from the Kaplan-Meier curves. They were not the second or the primary endpoints from the original study.

They are in this image-based criteria, and we only had 10 versus 20 percent. So this is from the Kaplan-Meier curves, and excuse for this confusion.

DR. MUCCI: My second question is, part of the efficacy -- and I think these were slides CE somewhere between 32 and 34, where sensitivity and specificity are considered. Yes, CE32, CE34.

We know from the data in the three studies under analysis here that virtually all biopsies turn out to be histology positive, whether they're fluorescent or non-fluorescent. So sensitivity by default can be anything you want to make it. The more non-fluorescent biopsies you take, the lower sensitivity is going to be. The fewer you take, the higher sensitivity is going to be.

So to me, the sensitivity and specificity

are, I think, somewhat misleading. The PPV and NPV are much more realistic.

DR. EZRIN: We appreciate the comment, and we agree that sensitivity and specificity are calculations, and as Dr. Stummer presented, dependent upon many factors, including location as well as presentation. They are calculated throughout the literature, and for that reason, our focus is on PPV.

DR. MUCCI: Yes.

DR. ROYAL: Dr. Gilbert?

DR. GILBERT: So I had questions about slide 16, specifically about the NIH Stroke Scale, and wanted to know whether you've looked at an analysis comparing those patients in whom the stroke scale declined. So they had neurologic compromise and their outcome specifically progression-free survival.

As a second, was there a correlation between those who were deemed to have a complete resection and a decline in the stroke scale?

DR. EZRIN: I will ask Dr. Stummer address

the data in CS-16. Slide up, please.

DR. STUMMER: Sorry. Perhaps could you repeat the first part of your question, please?

DR. GILBERT: Sure. So the first part was you have divided the patients into two groups, those who did not experience a decline in function as measured by the stroke scale and those who have. And was there an association between those who did have the decline and a prolongation in progression-free survival? And secondly, was there an association between those who had a decline and the likelihood that they experienced what was defined as a complete resection?

DR. STUMMER: I would like to first address the second part of your question because we're aware that going further might be inflicting damage. So what we also did -- and this is exploratory, if I may. We also restratified patients based on the degree of resection regarding the course of their NIH Stroke Scale.

I'd like to have the slide up, please.

So this is almost the full analysis -- I'm

sorry about this. This is a technical problem here at the top line here. But what the slide would show you, if you saw the top line, is basically that those patients, which have complete resections by MRI standards, actually do much better than those patients in the long run regarding the time to duration of NIH and overall event-free survival than those patients that had incomplete resections. You can also see this from the log rank test and also from the 6-month rate from these curves.

So overall, having greater resections in the context of malignant glioma actually gave the patient some form of benefit.

Regarding your first part of your question, I couldn't answer that question specifically because we don't have that analysis made in this form. I think it's an excellent question, but I can't get back to that at the moment.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: Thank you. I have just something first to confirm, that the endpoint, quantitative endpoint that you use as

progression-free survival -- sorry, PPV on a biopsy-based analysis, my impression from reading this is that for studies 28 and 30, these were in fact only secondary endpoints, and for the pivotal phase 3 study, number 3, PPV biopsy-based wasn't even a secondary endpoint.

Are those interpretations correct? And then the selection of PPV biopsy-based as primary endpoint was done all post hoc for the three studies, 28, 30, and 3.

DR. EZRIN: I understand three parts to your question. I'll break them down such that my colleagues and I can address them. They are biopsy based, although within the NDA, we present both at the biopsy, individual biopsy level, and at the patient level. What we presented today is biopsy based. It is my understanding -- I'll confirm with our team in a moment -- that, on 28 and 30, these were primary endpoints, and the statement in the study 3 is a post hoc analysis.

Allow me to confirm for one moment.

As the CEO of the company, I'll go to the

experts. Let me ask Dr. Moore to answer your question.

DR. HERSCOVITCH: Sure.

DR. MOORE: Anna Moore, project manager from Photonamic. Indeed, biopsy-based PPV in study 28 and 30 was a pre-defined endpoint, but it was the secondary endpoint. So your assumption was correct.

The primary endpoint in these studies were patient-based PPV, and for the NDA, we decided to use the biopsy-based PPV.

DR. HERSCOVITCH: Thank you for clarifying how these studies were initially laid out versus the data that you're now presenting.

I have a question regarding safety, and I'm actually looking at data, if I'm allowed to, on page 21 of 24 of the FDA package. Specifically with regard to table 15, Summary of Common Neurological Events, two of them, which might be considered a little more of note, were of greater frequency in the ALA-exposed patients. Specifically, aphasia occurred twice as commonly,

12 versus 24 patients, and hemianopsia occurred three times as commonly, 8 versus 23 patients.

Actually, as opposed to some of the others, dizziness, headache, somnolence, which presumably all got better, what was the time course in resolution of these more serious neurologic events? Because in theory, they could perhaps be attributed to somewhat more aggressive surgery because the surgeons were actually able to visualize additional tumor for resection.

So what was the outcome in the two times or three times more frequent occurrence of aphasia and hemianopsia in the fluorescent-exposed patients?

DR. EZRIN: So instead of putting up table 15, perhaps we can go to the time course profile. And I'll ask Dr. Stummer to summarize that for us.

DR. STUMMER: Slide up, please. These are data from the NIH Stroke Score, which was our most sensitive score for defining or assessing neurosurgical function in these patients. And this is time on the X-axis and NIH Stroke Score on the Y-axis. And this of course subsumes also those

patients with visual field effects after surgery and also language disorders after surgery.

It shows you the entire range of these patients with every patient actually in these bars. And it gives you a feeling of how -- well, first you would look at the medians or the horizontal bars. They're the same prior to surgery. And then actually, the patients in the white-light arm get a little better, and the median is at 48 hours, whereas those in the blue-light arm are still at 1 in the median NIH score. Then, as you can see at 7 days, this moves down to zero median in both arms. And then they essentially taper off in their differences.

Specifically for visual field effects and language disorders, we did have 4 or 5 SAEs, so severe adverse events that were reported based on SAE for language. One of those was from the safety analysis. It that was actually the calvarium [indiscernible] that was operated on. He improved, and the second one also improved over time, and three remained the way they were.

I would like to call upon -- this is now getting into a little detail, but I would like to talk about this. Slide up, please.

Again, we're looking at the very, very sensitive NIH Stroke Scale to understand which patients were at risk when we're doing this surgery. And I would like to go in detail through this slide.

This slide shows you the NIH Stroke Scale that we picked up at 48 hours after surgery. And it shows you in the top row the distribution of the NIH Stroke Score deterioration as compared to prior to surgery by just one point or more. And it shows you that patients in the ALA arm had 26 percent, 0.2 percent deterioration in the NIH Stroke Scale as opposed to 14.5 percent.

Now, if you look at the bottom two rows, it substratifies the patients based on whether they had already had a deficit prior to surgery or not. So the first row is those patients that had no deficit prior to surgery, NIH Stroke Scale zero, and you can see there is no difference.

So these are not patients at risk in a greater way if they are operated on using 5-ALA than operated on using white light. If they had any form of deficit, so an NIH Stroke Scale of zero, which is the bottom row, then you can see that these are the patients that have a greater risk for the moment, 29.6 percent versus 11.7 percent.

So we know these patients. These are patients that have fixed neurological deficits, which shows us that the tumor is actually growing into an eloquent brain region. And we have now shown with the study that these are the patients that we have to be very, very careful about.

But this is medical judgment. This is what we surgeons are doing. This is the practice of medicine. This is what we're always going to be concerned with. It would be exactly the same question, did we have the MRI intraoperatively or the neuronavigation as an adjunct? So this is a medical judgment we are doing here.

DR. ROYAL: Dr. Toledano?

DR. TOLEDANO: Thank you. This is Dr. Toledano. I have two clarifying questions to build on Dr. Herscovitch's questions.

Doctor Professor Stummer, they are for you. On your slide CE-5, I just want to build on the role of PPV in the different studies just to clarify that the positive predictive value, especially at the biopsy level, was not a factor contributing to the EU approval.

DR. STUMMER: Yes, ma'am. That is correct.

DR. TOLEDANO: You've been talking about the NIH Stroke Scale and how deficits, pre-op deficits in the NIH Stroke Scale, can increase the risk of aphasia, or hemianopia, or other cognitive -- neuro, nervous system disorders. But when you talk about a whole scale that looks at a whole bunch of things, you're not specifically teasing out the aphasias or the hemianopsias.

So we heard particularly about the hemianopsias, but I don't recall hearing an explanation of what happened with the aphasic patients over time.

DR. STUMMER: I don't think we have at the moment available for you these data, where you look at the development of these patients over time.

DR. TOLEDANO: Thank you.

DR. ROYAL: Dr. Jacobs has a question.

DR. JACOBS: Yes. I had a question about the supporting literature. On slide CE-30 and 32, you presented PPV and NPV from 11 peer-reviewed articles. I would like to know if any of the patients in those articles are also in your database that you're using from studies 3, 30, and 28.

DR. EZRIN: Since it is Dr. Stummer's data, I'll ask him to address the question.

DR. JACOBS: I assumed it would be.

DR. STUMMER: Just I didn't acoustically understand your question. I'm very, very sorry about that. It didn't reach me down there.

DR. JACOBS: The question is, essentially, in the supporting literature, are any of the patients in those articles the same patients that are in studies 3, 30, and 28?

DR. STUMMER: No, no.

DR. JACOBS: Good.

DR. STUMMER: Two of my studies are in there, but these are studies we did a long time ago right before that, yes.

DR. JACOBS: That's all I wanted to know. Thank you.

DR. ROYAL: Dr. Roberts?

DR. ROBERTS: Yes. One of the presentations, I think there was the comment that the fluorescence helps neurosurgeons identify the difference between normal brain and tumor, and therefore helps protect functional areas such as adjacent cortical spinal tracts.

My concern is how do you interpret the fluorescence because typically, as we know with gliomas, it's infiltrating disease, and therefore, just because you see fluorescence doesn't mean there isn't normal brain in that area as well.

Also, we've had discussions already about patients with already deficits in certain functional areas, which means that there is

infiltrating tumor in that particular functional area. So therefore, that functional area would tend to fluoresce with your product.

So therefore, the neurosurgeon, while he's operating, could potentially be tempted to resect that tissue if the thought is in there, if they're thinking that this is the differentiation between tumor and normal brain.

So I guess I'm just wondering how is that addressed to neurosurgeons potentially in your course?

DR. EZRIN: Dr. Hadjipanayis?

DR. HADJIPANAYIS: Yes. That's a very important point. So as you mentioned and as we discussed, the biology of these tumors are highly infiltrative. And we depend on other types of tools during the surgery to really help us identify those pathways.

One of the things that we stress is that not all patients can have all their fluorescent tissue resected. So that comes back to neurosurgeon judgment, and it also comes back to the Medicines

Management Program we discussed, where these are some of the concepts we will go over in the education of neurosurgeons with fluorescence.

But another important point, too, is that typically the fluorescence will extend up to the contrast-enhancing rim. And I think that's our goal with surgery, and that's been our paradigm in the resection of tumors.

DR. ROYAL: Go ahead, Dr. Roberts.

DR. ROBERTS: What about the situation where there is fluorescence that extends beyond the area of enhancement?

DR. HADJIPANAYIS: Yes. We would again utilize our neurosurgical judgment and tools with electrophysiologic mapping and other methods to detect those pathways. And we would potentially leave that fluorescent tissue alone. We don't advocate for resecting all fluorescent tissue in all patients.

DR. ROBERTS: If you are in a situation where you're not concerned about functional abnormalities or functional deficits, would you

then advocate resecting that tissue that's beyond the area of enhancement?

DR. HADJIPANAYIS: So a good example would be a right frontal high-grade glioma in an area where there's no immediate functional tracts. Then there would be the opportunity for the neurosurgeon to perform the resection of the fluorescent tissue.

DR. ROBERTS: Thank you.

DR. ROYAL: Does anyone else have any questions? Ms. Arkus?

MS. ARKUS: Thank you. A technical question, in the study materials, liquid is to be taken 3 hours before the surgery, but 1 hour is when the fluorescence is maximized and 3 hours is the half-life. So I was curious about why the liquid is not taken 1 hour before the surgery.

DR. STUMMER: So if I may, I would like explain, again, how this works. The ALA is the drug which is ingested, which is just a prodrug. This goes into the tumor, and there it's taking up in the tumor cells. And there, it goes into hemimetabolism, and this takes hours.

This begins when we do our initial measurements on this and analog experiments. We saw the first signal after 3 hours, and we saw a maximal signal in 6 hours. From our other experiments that we did in humans, and in skin, and in blood, we know that the peak is about 8 hours.

So the discrepancy is that, of course, the ALA is in the blood right away, but it takes a while when it's taking up in the tumor cell for the tumor cell to build up protoporphyrin IX. And this peaks somewhere around 8 hours with a wide range in which we can actually work. That's why the timing is as it is.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: Yes. I would like a clearer description of what kind of training program the company would establish. What would be the criteria for training and deciding when the surgeons are appropriately trained?

DR. EZRIN: Excellent question. And we have the benefit of having the originator of the training program in Europe with us, Dr. Stummer, as

well as one of his several hundred trainees, Dr. Hadjipanayis, who has trained surgeons in the U.S.

Gentlemen, who would like to field the question? Dr. Hadjipanayis?

DR. HADJIPANAYIS: So we have trained I guess close to 100 neurosurgeons now, and we have now developed a seven-module series and educational program where neurosurgeons are introduced to the concept of fluorescence-guided surgery, dosing, and visualization of the fluorescence, and understanding some of the concepts that we're discussing today.

This is an educational program that has to be passed on each part. There's actually tests that the neurosurgeons have to take after going through each of these to advance to the next module.

Did that answer the question? Can you restate? I can't hear you. I'm sorry.

DR. JACOBS: I'm sorry. How extensive is the course? Are we talking a day or a week?

DR. HADJIPANAYIS: It's about a half-day with seven educational modules.

Would you like me to go through the modules? Okay.

DR. ROYAL: Dr. Zamorano?

DR. ZAMORANO: Yes. Another question to clarify some of the information about safety based on the slide CS-14. So with these patients with serious adverse effects, is it possible to comment in this case what percentage of patients have tumors in eloquent versus non-eloquent areas. And also, as in the next slide, CS-15, there is a comparison of the patients with serious adverse effects in the control group and in the 5-ALA group.

Was there any difference in these patients in terms of the surgical technique used? So in other words, a difference in patients with intraoperative monitoring or craniotomy? It's a question for the surgeons.

DR. STUMMER: I have to say that this study was conducted a number of years ago in Europe,

where I know that we weren't as frequently using intraoperative monitoring, mapping technology at all as we are today. And as I recall, this was not really standard at the time, and this might account for some of the neurosurgical deficits we are seeing here.

This is much different now. Visualization is still the same, obviously, but the safety measures we're taking to make safety safe is different.

So specifically regarding your question, there were no differences in the study group of the patients that we could detect regarding intraoperative monitoring, mapping, taking to the time, with the restriction that these were not as commonly used as they are being used today. As Dr. Brennan mentioned, we are learning as we go.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: I would like actually to follow up on Bonnie Arkus' question. What is the underlying biochemical difference in tumor cells versus normal astrocytes or neurons that results in

the increase accumulation of fluorescent tissue?

Is it a certain enzyme which converts it to the fluorescent species, or is it that the fluorescent species is retained in the malignant tissue? What is the understanding of why this actually produces a signal in malignant cells?

DR. HADJIPANAYIS: Great question. Slide up, please. There are multiple different theories on this. One of them that's been shown with gliomas is that there's an enzyme called ferrochelatase that allows the formation of hemoglobin with the addition of iron to protoporphyrin XI. That enzyme is present in lower amounts in glioma cells, which allows for the build-up of protoporphyrin IX.

Other mechanisms are decreased outflow of the protoporphyrin IX from glioma cells. That's also been shown. There's been some other enzymes, too, in the pathway that can be impacted in glioma cells. It's very impressive, though, how it does accumulate within glioma cells in comparison to other normal cells.

DR. HERSCOVITCH: So this is a follow-up question. There are lots of biopsies, and their predictive value showed this, where there was biopsy-positive non-fluorescing tissue, perhaps more at the margins.

Is this attributed to much less cell density, just giving it pink or nothing? Or maybe the cells haven't differentiated as much into being malignant ones, so the enzyme machinery is different, which would cause the absent fluorescence in the presence of a positive histology.

DR. STUMMER: It's related to a number of factors, as I know, so we have experimental evidence where we took biopsies and we measured the MIB index. The MIB index is an index of proliferation, and we also measured cell density.

We found that, independently, for another proliferation, it predicts fluorescence, and also cell density predicts fluorescence. And we have to know that using a surgeon microscope, we are seeing to a definite level of -- as I showed you in the

video, if we can see a definite level, we can make the distinction between the border in the millimeter range. When you use a spectrograph, we can go even further because we're picking up individual tumor cells, so this sort of tapers away.

So it's not that the protoporphyrin IX is not there. We just cannot visualize it using the microscope, but we know it's there. We can measure it.

DR. ROYAL: Dr. Byrne?

DR. BYRNE: I just have a question about the degree of fluorescence. So weak versus strong fluorescence seems to me a natural, necessary, but false dichotomy and what's really more of a continuous distribution of cell frequency. Has there been any effort to better quantify degrees of fluorescence?

DR. STUMMER: So neurosurgeons that know the method, they will say there is a pink component and there is a red component. And of course, your question was excellent. I couldn't see who

actually posed it because I was sitting here behind the wall, but it's a very good question.

We also addressed that specifically in our study 28. When we're making this distinction -- which I think is important because with the red, I showed you the 90 percent cell density would have been 10 percent cell density. It gives us additional information that we need. We are now getting close to something which might contain function.

So to objectively show that, this is actually something we can measure, we use spectrography in our study 28, the first measure -- to point out, the first measure, the intensity of the fluorescence. And we did find a very strong relationship between the measurement spectrographically and what we were seeing using our eyes for distinguishing the colors.

So yes, it's not really tapering away. There are two different compartments of tissue. One is a solid tumor, and the one is the infiltrating tumor with a high cell density down to

about 10 percent. That would be my answer.

DR. BYRNE: There is one follow-up question. The positive predictive value is about 95 percent on average. So there's 5 percent there where you're doing a biopsy, expecting tumor, and it's not.

Have you taken a look at those 5 percent of cases to find out why? What was it that made it fluoresce that wasn't tumor?

DR. STUMMER: So it was a small number of biopsies, and I would only rely on those we took in our supervised studies. And as I showed you with the movie, we're actually taking these right next to the area of fluorescence. So this very, very high resolution we're getting with this method also gives us a high resolution for actually doing the testing.

Thus, we'd like to say maybe it's just a sampling error, could be that that part is a sampling error. But it might also be that there are some changes in the composition of the brain right next to the tumor, which, reactive

astrocytes -- I don't know if that would lead to protoporphyrin IX, and in response to the tumor being very, very, very close.

From a surgical point of view, we're looking at millimeters. But as the neurosurgeons know, when using the CUSA, which is a device for resecting tumor, we are beyond that 1-millimeter range. We're going 2, 3 millimeters at a time.

So as a neurosurgeon, having used this for so many years, I'm always concerned, of course, when I'm doing surgery, but these few samples of falsely-negative fluorescence are not a major worry to me. We're driven by function also.

DR. ROYAL: Dr. Gilbert?

DR. GILBERT: Yes. So I want to get back to the issue of risk and benefit and specifically address data that you recently showed for one of my colleagues; and that was the difference in the decline in function as measured by the stroke scale between those patients who started out neurologically normal and those who started out with a neurologic deficit.

I'm not sure, but I would suspect that those with a deficit would imply that the tumor was approximating eloquent brain. So if we then making an extrapolation and say there is a difference in the risk between those with non-eloquently located tumors and those with eloquently located tumors, it seems like there's a concentration of increased risk among eloquently located tumors.

Since that risk actually of worsening was almost a third -- I think it was 29 percent according to the slide -- how do we reconcile that with the safety profile from a patient standpoint in looking at this technology?

DR. STUMMER: First of all, those 29 percent based on the NIH Stroke Score, which is a very sensitive sale, were temporary as I showed you. Most of them went away. But of course, there were several patients where they sort of stayed.

We cannot really reconcile that other than telling the neurosurgeon -- and this is probably valid for all the instruments we're using -- neuronavigation, intraoperative MRI, what

have you -- that there are risks involved when operating on an eloquent brain.

If we can identify those patients up front, which we do, if they have a fixed neurological deficit, I have to start pre-treatment. It's not going to be the edema that's causing, but rather structural infiltration.

Those are patients to be aware of, and this is also what's part of the training course, which is just helping surgeons be aware. This is common surgical knowledge. We just refresh their memories that when you operate on an eloquent brain, there's a fixed deficit, and you're going to have higher risks.

But again, overall, every single patient counts of course, but these are a small number of patients, and most of them get better right away.

DR. GILBERT: So I guess the follow-up question would be, then, you do incur a higher risk in eloquent brain with the use of the 5-ALA because the control of the white-light arm did not have anywhere near the same degree of -- or same

percentage of worsening.

So in the context of investigators who had been trained as part of the study, even with all the caveats that you've mentioned, there is an increased risk. Again, you do mention that there is recovery, but at least initially, there is some concern that the fluorescence led to removal of tissue, obviously a combination of tumor with functioning brain tissue. That's why you've got the deficit.

So going forward, how would you propose in the training course to reduce that risk?

DR. STUMMER: Right. This phenomenon, we learned about this in the context of a phase 3 prospectively randomized multicentric trial with 16 centers. We weren't aware of this.

Now, one of the results of the studies, obviously, is that we are now aware of, and we can address this in our training courses, and this is what we do. We show our survival curves. We show the safety data to the surgeons and say that if a patient has a fixed neurological deficit after

pre-treatment, indicating functional or structural involvement of the tumor in an [indiscernible] tract or brain, those are patients where you have to at least use monitoring or mapping to identify those structures during surgery, and that is how we address this in the training course.

These are data we provide from this phase 3 trial. I would like to remind you these were the first patients that were ever operated. I think going on now with many, many, many patients, we would do a completely different setting nowadays.

DR. ROYAL: We are 35 minutes behind schedule. I'm going to take one more question. There will be a chance for more questions later in the day.

Dr. Toledano?

DR. TOLEDANO: This is Dr. Toledano. I'd like to change my question. Given that we have a chance for more questions later in the day, should we take our break?

(Laughter.)

DR. ROYAL: I'm not sure I understand your

question. Are you suggesting that we don't take a break right now?

DR. TOLEDANO: No. I'm suggesting we take the break since we can ask our questions later.

DR. ROYAL: If you would like to postpone your question, that would be fine.

DR. TOLEDANO: Lovely. Thank you.

DR. ROYAL: So let's take a five-minute break. So it's 11:07. So 11:12, if we could all come back here.

(Whereupon, at 11:07 a.m., a recess was taken.)

DR. ROYAL: If committee members can take their seats so that we can get started. We will now proceed with the presentation from the FDA. Dr. Ballard will begin.

FDA Presentation - Betsy Ballard

DR. BALLARD: Thanks, everyone, for coming. I'm going to be presenting the clinical review of this NDA. The proposed indication that the sponsor has given us is that it's to be indicated as an imaging agent to facilitate the real-time detection

and visualization of malignant tissue during glioma surgery. The proposed dose is 20 milligrams per kilogram administered orally 2 to 4 hours prior to surgery.

When we evaluate new drugs for imaging agents, we have several indications that we commonly use to approve drugs. They are structural delineation, or in this case, visualization, disease or pathology detection or assessment, the functional physiologic or biochemical assessment, and diagnostic or therapeutic patient management.

We require substantial evidence, which is defined in the regs as evidence consisting of adequate and well-controlled investigations. The FDA has generally interpreted this to mean that we require two adequate and well-controlled trials, each on its own convincing to establish effectiveness and safety. However, there are occasions when, based on relevant scientific data, one adequate and well-controlled study may be sufficient to establish effectiveness.

Simply generating an image for which the

implications to the patient are not understood does not necessarily confer benefits to the patient. Therefore, establishing effect of a medical imaging agent often requires data and other information on precision and accuracy as well as the clinical value of using the agent.

Approval of medical imaging agents need to provide accurate, reliable information that facilitates clinical management. Examples of this would be helping to make an accurate diagnosis or contributing to a beneficial clinical outcome.

The usefulness of an imaging agent may be self-evident, and clinical usefulness can be established by direct demonstration from clinical studies or reference to historical data.

What clinical outcomes could support clinical benefit? My part of the presentation is going to focus on the clinical aspect of this and Dr. Mucci is going to address the efficacy portion.

An agent designed to enhance visualization of tumor cells may require supportive evidence of clinical usefulness, and from these trials, we've

been able to tease out extent of tumor resection, patient survival, and patient function.

A preliminary assessment of the data showed insufficient evidence to suggest clinical outcome improvements when we looked at progression-free survival or overall survival. So the focus of this application is on the evidence needed for an indication of improved visualization based on the concordance between histopathology and tissue fluorescence. The clinical outcome data that's available from trial 3 will be examined to help support that claim of improved visualization.

I'm going to talk about some of the clinical outcome endpoints. The efficacies, as I said, will be discussed by Dr. Mucci. This is going to include the results from the trial as well as literature studies. And then the safety data comes from the clinical studies and the postmarketing experience that you heard presented.

The statistical presentation is going to concentrate on the visualization indication, and in our presentation, they're going to talk about the

positive predictive value, the false negative rate, and other exploratory analyses they've done.

Let's start with efficacy. The sources of data that we used to look at this are two phase 2 trials and one phase 3 trial. Those are 28 and 30, which, as you've heard, are phase 2 and study 3, which was a phase 3 trial. These included patients with newly-diagnosed and recurrent disease. There is a clinical safety database of about 550 patients and also support from a review of the literature.

There are common characteristics in all of these three studies, as you've heard. After the biopsies were taken, the surgeon did estimate or assess the extent of resection. They were specifically asked was the remaining fluorescence residual fluorescence and did that area appear abnormal or normal under white light.

They described the anatomical area of the remaining tumor. They estimated the volume of the remaining tumor, but the design did not allow for control of ascertainment bias. They did have central neuropathologic and neuroradiologic

assessments that were blinded.

As I said, all of them included newly-diagnosed patients, except for study 30, which was focused solely on patients with recurrent disease. The tumor grade was generally not known at study entry, and this is because these patients were entered into the study based on MRI characteristics. However, for the efficacy data, only patients with grade 3 and 4 gliomas were included.

In study 3, which is the only randomized controlled trial, the clinical outcomes data are going to come from this because this allows us a comparison between the control arm and the treated arm.

It was prospective. It was randomized. It was multicenter, and the control was standard operating conditions or what we're calling white light and fluorescence.

The study endpoints for the original trial, as you've heard, were completeness of resection, which was defined as the percent of patients

without contrast enhancement on MRI, so it's a surrogate endpoint, and also progression-free survival at 6 months.

The biopsy selections in this study were done irregardless of their fluorescence capability. The surgeons were allowed to alternate during the course of the procedure between white or blue light as they felt necessary. And it was a geographic assignment of biopsy regions, so they were told to biopsy the tumor core, the tumor margin, and distant from the tumor. And these areas were then assessed as to the intensity of the fluorescence.

The first thing we're going to look at is the extent of tumor resection. I'm going to refrain from calling this complete resection because the infiltrative nature of gliomas, we know that it extends beyond radiographic and clinical evidence of the primary mass. So the surgical procedure is usually a debulking procedure rather than what we would traditionally think of as an oncologic resection to clear margins.

There are a lot of factors that influence

tumor resection: tumor size, location, and proximity to eloquent areas, as we've heard. And the assessment of the extent of resection was, again, based on postoperative MRI. And it was defined as an absence of residual contrast enhancement in comparison to the pre-operative image. It's critical to understand that complete resection by MRI does not correlate with histologic absence of tumor.

So when you look at the volume of the tumor pre-operatively in this study, you can see that it was well stratified. They're pretty much equal in both the control arm and the drug arm.

When you look at localization, there were fairly equal numbers of patients who had tumors that were deemed to be in eloquent areas in both arms as well as those in non-eloquent areas. It was important to understand that regardless of whether it was felt to be close to an eloquent arm, these patients all had to be deemed resectable on the pre-operative MRI.

The one difference that is noticeable here

is that tumors close to the optical tracts, there were almost twice as many in the fluorescent arm as in the control arm.

The completeness of resection, when we look at this, basically we concur with the company. In the fluorescent arm, there were about 64 percent of these patients who demonstrated to have completeness of resection on the post-operative MRI. That's compared to the control arm, where the completeness of resection was only about 38 percent.

We're going to look at patient survival. This can be influenced by a variety of things, and typically, the post-operative treatments that these patients are offered will influence the progression-free survival and overall survival.

The patients were supposed to receive standard radiation therapy and some of them chemotherapy. However, as we all know, when you deal with patients, not all of them will follow through and get the subsequent treatment that they're required to have.

Tumor progression was defined as the occurrence of new tumor or an increase in residual volume of tumor of greater than 25 percent on a subsequent MRI. And the data here, the progression-free survival was 36 percent in the treated arm versus 22 percent in the white-light arm. The Kaplan-Meier curves that were generated by the sponsor for overall survival basically show very little difference between the two arms.

So we look at additional literature support. The sponsor gave us 12 publications to look at and the PMA report from Japan. The methodology used to determine which papers would be supportive, they had to have reported on the biopsy-based positive predictive value.

There had to be a surgeon's assessment of fluorescence during resection. And preferably, they wanted papers where the resection was completed under white light prior to switching to fluorescence, but they did allow papers where the surgeon switched between the two.

We ended up with 11 single-arm prospective

studies: two required complete resection under white light followed by fluorescence; six of the studies allow the surgeon to switch as desired; and the remaining three had no mention of when the fluorescence was used.

These patients had both primary and recurrent tumors. In some of these papers, the 5-ALA was also used in conjunction with other intraoperative assessment methods such as intraoperative MRI, neurophysiologic mapping, or ultrasound.

When we look at the results of the literature -- I think you've seen this slide before -- it shows consistently that the positive predictive value in all of these studies is extremely high. The negative predictive value has a wide range from a low of 26 to a high of about 67 percent. And this goes to, as we've heard, in terms of where the biopsies are taken from.

Ideally, we would like to have patient-reported outcomes as an assessment for if there is a true benefit to patients. This might include

things such as reduction of steroid use or reduction of anti-epileptics and also quality-of-life measures. However, we don't have these in these studies. And to the best of my knowledge, there are very few studies in the literature that actually provide these types of outcomes.

So what we're looking at for patient functional outcomes are basically the Karnofsky performance status over time. And you can see that there's really very little difference. These patients all had to be higher than 70 percent for entry, so the median values were fairly high to start with, and over time, they basically stayed the same. So for patients who were alive, they really didn't show a deterioration.

When we look at the NIH Stroke Scale, this is just another way of looking at what we've already seen, it shows that usually, in the immediate post-operative period, the treated arm seemed to have a worsening in their NIH score. However, that resolved back to baseline and remained the same.

It's important to note that the NIH Stroke Scale is an assessment of motor, sensory, and speech, as well as the standard neurologic signs when you're doing a neurologic exam. And the scale goes from 0 to 36. So most of these patients were fairly low to begin with. And although they deteriorated briefly, it was a temporary change, and they returned to baseline.

As far as the safety evaluation is concerned, the database for the safety analysis includes two additional studies, ALS-8 and ASL-32. They were divided into drug-related adverse events and procedure-related adverse events.

Just as a brief background, study 8 is a single-centered dose-finding study. It was also uncontrolled, and there were 21 patients involved in that. They were given 20 -- they were given multiple doses. And the patients that were given the 20-milligram dose were the ones that were included in the analysis.

Thirty-two was a prospective single-arm multicenter study looking strictly at safety of 5-

ALA for patients. There were no efficacy endpoints in this study, and they contributed 243 patients to the database.

So when we look at the summary of adverse events, you can see that serious adverse events were fairly similar between the control arm and the drug arm. There were very few serious adverse events. The majority of adverse events were grades 1 and 2.

When we look at ALS-3 alone, you can see that control arm had greater amounts of grade 1s, but again, grades 3 and 4 were fairly similar, a little bit more grade 4 in the fluorescent arm mainly because there were some immediate deaths in that arm that were not due to the drug.

The drug-related adverse events that are identified both in these studies and in the literature are photosensitivity and photodermatosis, GI complaints, nausea, and diarrhea. We can see evidence of hypotension in these patients, an occasional report of hypertension. There's a transient elevation in

liver function tests and pyrexia.

When we look at the procedure-related events -- and this accounts for the vast majority of the adverse events that were seen -- you see thromboembolic events, DVTs, and pulmonary emboli. These are not uncommon events in patients with malignancies and undergoing surgical procedures.

The cardiac and hematologic events that we saw in this study were things like thrombocytopenia, leukocytosis, a drop in your hemoglobin and hematocrit. And these are also things that commonly occur after surgery.

Pulmonary events, several causes of death were due to pneumonias. These patients may or may not be on ventilation in the intensive care unit for prolonged periods of time. But the most important one are the neurologic deficits. And we saw motor, visual, and speech deficits, and then brain edema, seizures, and transient alterations in cognitive function.

So it's a busy slide, but when I tried to sort out and group together some of the neurologic

deficits across all five studies, you can see what they are. And as already has been pointed out by previous questioners, the rate of aphasia and the rate of hemianopsia was higher in the treated arm than the control arm. However, over time, a lot of these deficits did resolve.

There's a periodic safety update that was provided to the European Union in 2015. That's where the estimated cumulative number of patients receiving the drug is 58,000. And in that report, there are no reports of unanticipated adverse events.

The sponsor has proposed a 5-ALA training program for the neurosurgeons. The program emphasizes information on techniques to optimize the use of 5-ALA fluorescence-guided surgery. It does not mitigate a drug risk. Therefore, it is the FDA's conclusion at this time that we are not considering a training program as a risk evaluation and mitigation strategy.

In conclusion, the patient data outcomes are generally supportive of the proposed visualization

indication. Data from the publications provide a description of the information and visualization of performance of 5-ALA, and the safety profile of 5-ALA is generally acceptable for its proposed clinical use.

FDA Presentation - Anthony Mucci

DR. MUCCI: I am going to unfortunately put you through some of the things you've been through three or four times already today, designs, and after that, I'll really get into the statistical information.

There's an outline here. Studies under statistical review will first be presented, an overview of the study designs, which we've already seen, but I'll go into a little more detail. Then there will be a focus on the primary endpoint, which is positive predictive value, but then an equal amount of time will be given to the false negative value. And then there will be some exploratory analyses.

The three studies we've already talked about -- so I'll skip over this slide. We know

these as study 28, study 30, which are phase 2 trials, small numbers of patients, 30, 36, something on that order. And then the single phase 3, which is the prospective randomized group sequential rater-blinded study.

I want you to note here that these studies were conducted between 1999 and 2005. Study 28, patients had newly diagnosed unilocular malignant glioma for which surgery was indicated. In order to get into the full analysis set, there had to be verification that the tissue was grade 3 and 4.

Tumor resected under white light, then biopsies were collected. I assume they're collected after the resection. There were non-fluorescent, weakly fluorescent, and strongly fluorescent biopsies. The intention was to obtain two non-fluorescent biopsies, three weak fluorescent biopsies, and three strong fluorescent biopsies. The median number of fluorescent biopsies was 6; non-fluorescent biopsies was 4.

Biopsies were afterwards classified as positive and negative by histology and completeness

of resections determine by a central read of an early post-surgical MRI.

The original endpoint here was a patient-level positive predictive value. That is, a patient was scored as successful if all of the fluorescent biopsies turned out to be histology positive. So if you had 8 fluorescent biopsies, all 8 had to be histology positive.

The secondary endpoint, which was biopsy level, was simply the percent of histology positives among the fluorescent biopsies. And as we've already heard, that became the primary endpoint for the NDA.

Study 30 differed from study 28 first in that the patients had recurrent glioma. Another way in which they differed was how the biopsies were taken. After the resection, but still under white light, an area was found that was white-light normal by the surgeon, and an area was found that was white-light abnormal by the surgeon. This had nothing to do with the fluorescence.

It was then that fluorescence was employed

in order to obtain strong fluorescent biopsies and weak fluorescent biopsies. And there were a few non-fluorescent biopsies. As was mentioned before, I think there was a total of 16 non-fluorescent biopsies. The median number of fluorescent biopsies was 11.

Then we come to the phase 3, the same inclusion criteria. What was different in the collection of the biopsies here from the other two studies was, prior to resection, three areas were chosen for biopsy. One was the core, one was the margin, and a third area was what is called distant.

So in general, although I've listed means here, mean fluorescence being two, one weak, one strong, and mean non-fluorescent being one, virtually in all patients there were exactly three biopsies.

Afterwards, of course as with the other studies, we had biopsied tissue classified as positive or negative, also completeness of resections determined by a central read. But there

was also a follow-up with the patients for progression-free survival, which was evaluated at various times, but most critically at 6 months.

This study had original primary endpoints. One was the percentage of patients with complete resection early post-surgery MRI, and the second was the percentage of patients who were progression free at 6 months post-surgery.

Now we turn to the primary endpoint, the positive predictive value. All previously mentioned endpoints became secondary. The positive predictive value here is at a biopsy level. It's percent of fluorescent histology-positive biopsies.

In our analyses at the FDA, we decided to focus also on a complementary endpoint, which we're calling the false-negative rate for fluorescence, which is the percent of non-fluorescent biopsies that were histology positive. And this is equivalent to 1 minus the negative predictive value.

Some general comments about positive predictive value, it's dependent on the prevalence

of the disease condition. High prevalences typically produce high positive predictive values. In these studies, as I've mentioned, this PPV is assessed in conjunction with at least one additional complementary endpoint, the false-negative rate. There is a concern here that although the PPV is very high, the FNR is also quite high.

We looked at three definitions of positive predictive value, the biopsy level, which I've already mentioned, and the accompanying false-negative rate. Then we looked at within-subject-level biopsy level, which is you do what you would do in the first case, that is it's a percent of fluorescent biopsies which are histology positive, but you do it per patient, and then you average over all patients.

There was a third positive predictive value, and that was the sponsor's original one, which was the one in which a patient was scored as a 1 if all fluorescent biopsies were histology positive. This is very stringent. If you had 8 fluorescent

biopsies, all 8 had to be histology positives. And that will not be focused on here.

Here's the first table. If you look at this table, the emphasis should be to the left in red. This is the positive predictive value at the biopsy level for the three studies. You see that in the phase 3 study, the PPV was 98 percent, n study number 28, it was 96 percent, and in study 30, it was 97 percent. So virtually every fluorescent biopsy was histology positive.

If you look at the within-subject positive predictive value, it's virtually the same as the overall biopsy level. The subject level you see starts moving down because of what I mentioned, all the biopsies had to be histology positive.

But now, let's get a little more granular. Although the studies record fluorescence as none, weak, and strong, they also record histology according to cellularity, from 0 percent to 100 percent. And only 0 percent was considered negative. If you had 1 percent cellularity, you were positive for histology.

The next table refines the previous table to reflect these levels. I'd focus on overall findings down at the bottom. If you look at where there was no fluorescence in the biopsy, you'll see that 66 percent of those biopsies turned out to have histology levels of cellularity between 1 and 50 percent.

So the focus there, if you were non-fluorescent, you'd find mostly 1 percent to 50 percent histology of cellularity and a total of close to 80 percent histology positives. There was only 21 percent of these non-fluorescent biopsies, which were histology negative.

If you look at the weak fluorescence biopsies, you'll see that the histology moves over to the greater-than-50-percent region. Sixty percent of the cellularities for the weak fluorescent biopsies were greater than 50 percent. There's 35 percent, approximately one-third of these, that histology had cellularities between 1 and 50 percent. The strong fluorescent biopsies were overwhelmingly high cellularity, greater than

50 percent.

Now, let's look at fluorescence versus tumor type. Strong fluorescence corresponded to solid tumor. Weak fluorescence corresponded either to solid tumor or infiltrative tumor. And weak fluorescence was more likely in areas at the tumor margins. However, in areas of non-fluorescence, tumor was also likely to be present, largely infiltrative.

This table refers strictly to the phase 3 study in which I looked at core, margin, and distant. Remember, those were the three places where the biopsies were taken. And I looked at the combinations of fluorescence level and histology.

Now, if you look at the core, 82 percent of the biopsies were strongly fluorescent and histology positive. The only other category there that shows up at all is weak fluorescence and histology positive. But basically, at the core, you're talking about strong fluorescence and positive histology.

If you go to the margin, there's a

concentration on weak fluorescence and positive histology, 83 percent there, marginal everywhere else. If you go to the distant biopsies, they're concentrated on non-fluorescence, but also histology positive.

So the first take-home message from this slide is virtually every biopsy was histology positive. And the other message here is that, if you are in the core, there's strong fluorescence, if you're at the margin, there's weak fluorescence, if you're distant, there's no fluorescence.

We'll take this a little further and look at complete resection. Up to this point, I've just talked about the predictive values. This was mentioned before, complete resection rates in the phase 3 study. In the 5-ALA arm, it was 64 percent. In the control arm, it was 38 percent. This is a statistically significant difference. The difference is 26 percent. I have a 95 percent CI here, which is a normalized approximation. I think it differs a little bit from the sponsor's, but it doesn't matter. It's overwhelming.

How do we relate fluorescence to complete resection? Here, we're looking only at the 5-ALA arm of the phase 3 study. The analysis here showed that the non-fluorescent tissue was histology positive for 4 out of 5 patients.

Now, I make some assumptions here. The assumptions are non-fluorescent tissue was not resected, and the other assumption is that the MRI enhances histology-positive tissue, which we assume.

If these two hypotheses are in place, then complete resections on histology-positive patients should be less than complete resections on histology-negative patients.

This is a subset of that data, that I had available for making this analysis. There were 137 patients out of the 176 on which I could do this. If you look at the patients with negative histology on their distant biopsies, the complete resection rate was 41 percent. If you look at the patients with positive histology on their distant biopsies -- and remember, all of these biopsies are

non-fluorescent -- the percentage of complete resections was 36 percent.

So there appears to be no significant statistical difference between the negative histology and the positive histology patients, all of whom were non-fluorescent for distant.

Observations that I want to make here, complete resection rate, as I've said before, on the 5-ALA arm was greater than complete resection rate on the control arm. But for the 5-ALA arm alone, fluorescence level was determined almost entirely by biopsy site, histology was determined largely to be positive regardless of biopsy site, and the complete resection level for patients whose non-fluorescent was histology negative was about the same as the complete resection level for patients whose non-fluorescent tissue was histology positive.

Concluding remarks, PPV was very high, but the complementary biopsy-level false-negative rate was also very high; 4 in every 5 non-fluorescent biopsies were histology positive. The intensity of

fluorescence correlates with tumor cellularity. The 5-ALA arm results did not provide for a direct link between PPV and complete resection.

I want to emphasize here that there was a difference between the control arm and the 5-ALA arm in terms of complete resection. The difficulty was in tying that difference to the positive predictive value or the negative prediction rate.

Added value of a new diagnostic should be its ability to correctly classify disease state in cases where standard diagnostics are uncertain.

The diagnostic differential of fluorescence is not clear from the phase 3 study. First of all, it can be predicted by biopsy region, and region corresponds more closely to histology than does fluorescence.

So the added value of the 5-ALA fluorescence is more directly addressed by increased complete resection when you compare the test arm to the control arm, which might be biased because of the absence of operator blinding and study design. And that's it.

Clarifying Questions

DR. ROYAL: Are there any clarifying questions for the FDA? Please remember to state your names for the record before you speak, and if you could turn your name card, that would be helpful to me. Dr. Frank?

DR. FRANK: Yes. This is a clinical question, so it may be unfair to put it to a statistician. But by pointing out that the fluorescent-negative regions were histology positive, are you suggesting that perhaps the surgeon should have known that, would have operated that area had it been fluorescent positive, and has missed the opportunity to resect histology-positive area?

DR. MUCCI: You're right. It's not a question for a statistician.

(Laughter.)

DR. FRANK: I think I made the point by asking the question.

DR. MUCCI: All I can say as a statistician is I think they wanted to get a fairly broad

sample. And the assumption was that if you're distant from the core, you're going to have non-fluorescence. What the histology would be is anyone's guess, and it turned out to be positive.

But maybe Betsy can answer that.

DR. BALLARD: Can you repeat the question again?

DR. FRANK: So my question is, by pointing out that fluorescent-negative biopsies distant might be histology positive, is the suggestion that the surgeon should have gone there?

DR. BALLARD: Ideally, if this was a perfect world and we didn't have to worry about other things in the brain, the answer to that question would be yes. However, because of the area that we're operating in, you have to make judgments based on the location of the tumor.

Even though you know that there may be positive fluorescence left behind, it may not be in the patient's best interest to resect that area of tumor. And that's why it's a particular problem when you're operating in the brain. If we were

using other types of solid tumors, it may be less of an issue.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: Thank you. I just have a question about my understanding of selecting outcome measures. And biopsy-level positive predictive value was only a secondary in the two smaller studies and wasn't even an endpoint in the larger phase 3 study. But the sponsor went back on a post hoc basis and did careful calculations of biopsy-level PPV.

Now, at least in my simple-minded understanding of statistics, when you do something different than what you originally designed a study to do in terms of endpoints, and in fact when you pick an endpoint that wasn't even mentioned in the study, as happened in study 3, does it detract from the conceptual statistical strength of your analyses as opposed to using the primary and perhaps secondary endpoints that you specified to begin with?

Is that poor statistical practice, or does

it cast any concern about the data? That's one question I have.

DR. ROYAL: Dr. Mucci?

DR. TOLEDANO: Hi. This is Dr. Toledano. Dr. Mucci is passing it to me. So with any well conducted study, you have a prespecified plan, prespecified stop plan based on the endpoints.

Sometimes, as you're enrolling the patients and you're still blinded to the data, science changes. So you may update your plan before the data locks and comes to you as the statistician.

But other times, as we see here, you already know what happened for the planned endpoints, so you're making these post hoc analyses, and then you do have to be careful about why you chose those particular post hoc analyses and whether that was objective.

So maybe that gave you enough for Dr. Mucci to take off one.

DR. MUCCI: -- a particular one.

The emphasis here would be on visualization, and certainly in the phase 3, the PFS is not a

visualization endpoint. So if you're going off for a visualization, you might have to go back and replace some clinical endpoint with a visualization endpoint. But this is really the sponsor's ballgame, not mine.

DR. HERSCOVITCH: I'm sorry. Just a couple more questions. There is a table on page 16, table 5, which compares for histology-positive and histology-negative biopsies, how the white light did versus the fluorescent.

If you look at the diagonals and the off-diagonals, it appears -- and maybe the FDA staff can tell me if I'm correct in interpreting that table. It appears that page 16 of 24 -- and that's table 5 just at the bottom. This is in the briefing materials.

DR. MUCCI: Yes. This is where we have core, margin, and distant?

DR. HERSCOVITCH: No. This is page 16 of 24, and it's table 5 biopsy-level data. Table 5.

DR. MUCCI: And this is from the clinical review

DR. HERSCOVITCH: This is FDA MIDAC briefing document page 16, at the bottom.

DR. MUCCI: Let me see it.

DR. HERSCOVITCH: It appears, for both sides of the table, that the white-light and fluorescent-light biopsy evaluations were really identical. And if anything, the white light appeared a bit better if you look at the top cell second from the left. It just appears that there's no difference at all between using fluorescence or not using fluorescence and just using white light if you look at the diagonals and the small number in the off-diagonals.

Is that a correct interpretation of that table?

DR. MUCCI: Maybe another way of saying it -- and maybe this is what you're inferring from that -- is virtually all biopsies were positive. I mean virtually. If there was fluorescence, it was almost 100 percent. If there was non-fluorescence, it was 80 percent.

Is that what you're observing here?

DR. HERSCOVITCH: Right. But I'm also observing no difference between white light and fluorescence in general because the diagonals have high numbers, and the off-diagonals are very small. So that seems to me a very, very high concordance and the fact that the fluorescence didn't add much to a white light evaluation on a per-biopsy basis.

DR. MUCCI: Yes. But I'm still uncertain as to how white light made these classifications.

Does the other side of the room know how that was done? Calling a biopsy positive or negative under white light, it wasn't clear to me reading through any of the documents how that was done.

DR. STUMMER: Our highly supervised study 28 and 30, in study 3, there was no supervision, and we made no prespecification about that because we knew that -- or we suspected that in the prospective multicentric setting with two surgeries per study site, we would not be able to control for that in any way.

So we are not focusing on location of these

biopsies. This was not controlled for. We did not know where the biopsies were taken in relationship to, and the contrast-enhancing tumor, you would maybe see.

So if we take the biopsy out of this part of the cavity and the contrast-enhancement tumor will be on this part of the cavity, we don't have any of that information relating to these studies.

DR. HERSCOVITCH: I have one more question. One assumes that there is some degree of confidence in the completeness of resection data. It was, like, 65 versus 30-something --

DR. MUCCI: Yes.

DR. HERSCOVITCH: -- as determined by contrast-enhanced MRI post-op, although everybody knows that there still is some infiltrating tumor on the borders. But I'd just like to ask about the use of progression-free survival because I believe one of the FDA presenters questioned it, although there are data. It was I think 35 versus 20 on the basis of imaging and 21 versus 11, I guess, if you include clinical and imaging.

So should we be giving weight to those results or not really on the basis of the FDA analysis?

DR. MUCCI: The FDA has focused on only those endpoints that involve visualization, but there are some backup slides. Should we just look at the backup slides?

DR. MARZELLA: In essence, we are focusing on the visualization endpoints, and the focus for the other endpoints is basically to view them as supportive and to see whether or not they trend in a general direction.

I think that given the lack of reliance on MRI outcomes as evidence of tumor progression, and given also that, to my reading, there was an adequate control of the post-surgical patient management, that we don't view those outcomes as being convincing enough to allow a claim of improvement in survival, that and also the lack of concordance between overall survival and progression-free survival.

So given those uncertainties, we looked at

basically clinical outcome data as being generally supportive and focused on the visualization claim. So objectively, what is the evidence that, based on histopathology, the fluorescence does what it's intended to do, which is to identify areas of tumor.

DR. HERSCOVITCH: But there was confidence in the completeness of resection data with the 65 versus 30 something.

DR. MARZELLA: Yes, yes. The numbers were verified.

DR. HERSCOVITCH: Thank you.

DR. ROYAL: Dr. Roberts?

DR. ROBERTS: Yes. My question to the FDA, we talked about positive predictive value and negative predictive value, but potentially more concerning would be the cases where the fluorescence was positive, but the histology was negative, and your analysis didn't focus on that as much.

In particular, even going back to the tables that you had discussed earlier, if you look at

table 7 with study 30, there was 11 cases where the white light was negative, and therefore the surgeon would potentially have stopped surgery. However, the fluorescence was positive, so that would mean the surgeon would continue, but the biopsy was negative.

So that would be 11 cases where the surgeon was potentially misguided to resect normal brain tissue. So I was just wondering about the level of concern by the FDA in those cases.

DR. MARZELLA: I think that is an unfair question for the statistician.

DR. MUCCI: It's not for me.

DR. MARZELLA: I think that the positive predictive value numbers are rather high for what we typically see for an imaging agent, but we view this as basically a risk-benefit assessment; what is the overall benefit, given the fact that there are some areas that are not in complete concordance with the histopathology?

So clearly, there is some concern, but we look to the overall evidence, the actual numbers as

well as the clinical outcomes, to make a risk-benefit assessment.

DR. ROYAL: Go ahead. Dr. Roberts. Sorry.

DR. ROBERTS: Sorry, one more question. Also, given the fact that children also present with high-grade gliomas and other tumors where extent of resection is important, I'm just wondering about the lack of pediatric data in this.

DR. BALLARD: The normal criteria for all of these patients were ages 18 and over. So there were no pediatric patients involved in these studies. So we don't have any data to address the pediatric population, even though they can harbor malignant gliomas.

DR. ROBERTS: Right, yes. I was going to ask that question to the sponsor earlier why pediatric patients were excluded.

DR. MARZELLA: Given that this is an orphan indication, there's no requirement that there be a pediatric study, but we would invite obviously the sponsor to look into this because there may be some value clearly in this pediatric patient population.

DR. ROYAL: Dr. Hackney?

DR. HACKNEY: This is a broad question to the FDA about what significance we should attach to the histology findings. My take on it is that, without any data, if you ask me what do you find if you biopsy the brain in progressively farther-removed locations around a malignant glioma, my answer would be tumor cells, fewer as you get farther away. And nobody ever intends to resect every tumor cell from someone with a malignant glioma.

So the finding that you typically get some tumor cells and therefore, by definition, positive biopsies in areas that are fluorescent negative is exactly what you would hope for if you have something that isn't going to tell you take out the entire brain.

So I guess I'm not sure how much attention I should pay to that whole question. It might have been interesting if there was very little relationship, if they were finding lots and lots of areas that seemed randomly related to whether there

were tumor cells. But given the biology of the tumor at hand, it seems to me there couldn't be any other finding than the ones they came up with, which is a very high level of positive biopsies in the vicinity of malignant tumors.

So my question is, should this factor into our decision-making? It seems there's not much actionable information here.

DR. MUCCI: I'll address part of that, but I'll address it from a purely logical point of view, not even statistical.

If you have some validation, which is almost always on one side, histology positive, then it becomes difficult to see how it allows you to have any differential effect whatsoever.

DR. MARZELLA: So that is precisely the reason that we are convening here, because it is a very difficult situation. Given that the tumor is so infiltrative, what is the value of trying to add fluorescence visualization?

I think that, clearly, there is a correlation between the extent of cellular

infiltration and the intensity of the fluorescence. So there would seem to be some validity to this observation.

In this particular context, we're asking the experts whether, in your view, this would be a useful tool given that the biology of the tumor is such that we're not dealing with curative resection. We're talking about debulking.

So we have a great deal of difficulty in trying to assign a value to additional debulking, if you will, and so you are focusing on really the critical question that we're struggling with.

DR. ROYAL: Dr. Gilbert?

DR. GILBERT: So I would like to continue just a little bit on this issue of histology and fluorescence and ask the converse question, which is the situation where the fluorescence was absent, and yet the histology data showed a very high percentage of tumor cells.

So as opposed to Dr. Hackney, who pointed out appropriately that there is a gradient, what advantage is there if in fact dense tumor

cell -- and we have that data from slide 17 from Dr. Mucci's presentation where 13 percent had a high density, yet no fluorescence. And that would obviously be an area that would not be subject to resection based on the criteria.

So yes, we know they're infiltrative, and what's your threshold? We know that when there's been attempts to be overly aggressive with surgical resection, it's been detrimental to patients, but this is the converse.

So how should we look at this as far as the sort of risk to benefit in the context of this technology?

DR. MUCCI: I would just have to reiterate that it seems the critical thing is the resection. And the difficulty is aligning the resection in anyway with the biopsies and the histopathology.

Clearly, in the phase 3 study, you have a control arm, and you see that the test arm certainly did better in terms of the complete resection. But then you go back and try to say, okay, we have better complete resections here. We

have an endpoint which is PPV or a complementary endpoint, which is false-negative rate. How do we tie those in with the complete resection? And this table indicates that there's some difficulty in tying them in. They might be tied in, but the particularly way in which it happens is not clear.

DR. GILBERT: Thank you.

DR. ROYAL: Dr. Toledano?

DR. TOLEDANO: Thank you. Yes. So this is Dr. Toledano, and I'm getting to my question. It's on slide 10 for Dr. Mucci.

One of the things that we've heard is that the studies happened a long time ago, and it's been at least 10 years since they even finished up. Is there any new knowledge to support replacing the original endpoints with biopsy-level PPV?

Part two, do you have concerns with using data collected for one set of endpoints to evaluate a different set of endpoints?

DR. MUCCI: I'm just the messenger.

DR. TOLEDANO: Well, thank you.

DR. MUCCI: This design comes from the

sponsor, not from the FDA.

DR. ROYAL: Dr. Jacobs?

DR. MARZELLA: I just wanted to comment earlier with regards to the comment on complete resection. I think the sponsor showed some correlations between extent of resection and survival, both in the randomized study, and that correlation was apparent in both the control arm and the experimental arm.

I think the FDA has validated those analyses. Obviously, they're exploratory, but they are just an attempt to try to make that correlation

DR. JACOBS: I have what I guess is really a philosophical question, which was induced by the last slide from the statistical review about the study being biased because of the absence of operator blinding in the study design.

Does the FDA have any knowledge of a way to blind a surgeon? I mean, one of the issues that we're dealing with here is that, even if you look at something and you know it's positive, you may not be able to take it out because of where it is.

So I don't quite understand how you could possibly do a blinded surgical study.

DR. MUCCI: Before I answer this, we will look at a backup slide.

DR. MARZELLA: While the backup slide is going up --

DR. MUCCI: Then we will have to go verbal. I think a direct answer to your question would be that the blinding is that the surgeon knows that he will not have access to the fluorescence, therefore he might be biased to be more conservative than he would be otherwise. That's one way you can look at it.

But there are alternatives to this that the FDA has been considering. And I don't know -- are we spelling this out here or is it on a different slide? Yes.

What you would do is the surgeon doesn't know, at the beginning when he's starting and when he's working on the white light, if he's going to have access to the fluorescence. You open an envelope and it says, yes, proceed to fluorescence

or don't. And that's the only way I can think of to get around this bias issue.

He doesn't know. The way these studies were conducted, if you're in the control arm, you know you're not going to have access to the fluorescence. If you're in this new design, you don't know. You don't know until you open that envelope, so you're going to do whatever you can under the white light.

DR. JACOBS: So you are saying, basically, you would do the equivalent of study design 3, but the surgeon wouldn't know which arm the patient was in, so --

DR. MUCCI: He wouldn't know which arm the patient was in.

DR. JACOBS: -- he could use the fluorescence or not, but if the patient hadn't been given the drug --

DR. MUCCI: Yes.

DR. BYRNE: If we could take a look at table 2 again, the fluorescence level versus histology cellularity. I just want to get back to

practical matters here.

From a surgical standpoint, we know that it's going to be diffusely positive where you biopsy. You could be an inch away and it might be positive, and it has nothing to do with MRI findings or fluorescence. That's a given in high-grade glioma.

I look at it as if you look at the overall findings, if you look at the statistics of fluorescence strong, histology greater than 50 percent, that seems to me to be the bullseye of what a surgeon is thinking about during surgery.

The histology 1 t 50 percent is a judgment call, and then the fluorescence none, histology none is also of some value. But if you looked at it from that standpoint, if you're looking at only the histology greater than 50 percent and strong fluorescence, is that statistically compelling to you?

DR. MUCCI: It's a strong correlation between the strong fluorescence and certainly the cellularity level. But if you look at study ALS-3

above, ALS-3 has a lot of patients. So the overall findings at the bottom is mostly reflective of the top.

On the top, this strong fluorescence was largely at the core. So basically, what that is saying is, if you're taking a biopsy from the core, it's going to have high cellularity. If you're taking it from the margin, it's going to be largely infiltrative.

DR. BYRNE: Right. And I understand and agree. I'm just trying to make it a practical view from the surgeon's view through the microscope, how a surgeon might use this as an imaging tool.

The issue about whether or not a biopsy remote is going to be positive to us is just a given. And there might be scenarios where the surgeon is looking through the white light and not quite seeing what they think they're going to see through white light or that might be of some value for the histology and the strong fluorescence.

I'm just looking -- I'm sort of turning it upside down and looking at where is it strongly

positive.

DR. TOLEDANO: This is Dr. Toledano, and I'll request that you please put backup slide number 3. And it's the backup slide number 3. This relates to a possible study design that could avoid or control operator bias, and it gets to this question of how surgeons would actually respond to fluorescence and the visualization.

If we do the study the way that it's outlined on the slide, we would know how everybody acts with white light under the presumption that they would never see fluorescence. But I don't know how accurate that would be in terms of showing the added value of fluorescence when they know they're going to get fluorescence.

Does the behavior of the surgeon change in white light depending on whether they get fluorescence? And if so, should we be looking at that instead of the not-change?

That's my question for Dr. Mucci.

DR. MARZELLA: If I may interject, I would like to go back to the question that was being

asked earlier in terms of visualization. I think the point of how to design a trial that would avoid operator bias, maybe we could reserve judgment on that, at least for the time being.

But the issue is that, for a visualization claim, the division does not require clinical outcome data, that there needs to be some level of supporting evidence that points to the value of the imaging agent.

In some clinical contexts, the value is obvious. If you take an x-ray picture and you see a fracture, you don't have to show patients that in fact the correct diagnosis done had a good clinical outcome.

So to be able to infer clinical value is -- if this was a curative tumor and we were talking about validating the extent of tumor-free resection, we wouldn't have a problem.

So we are looking at the fact that it is a disease, which is lethal, that there potentially could be some value in the ability to visualize tumor, and that we also are looking at an approach

that looks at the totality of the data to see whether in fact there is increased extent of, quote, "complete resection."

We looked for other clinical outcome data to see whether or not it was trending in the correct direction. We also look at a risk-benefit consideration. What is the potential for harm for the drug or potential for over-aggressive surgery?

So it's a difficult decision, but I wanted to make the point that, for a visualization claim, the thing that we would focus on would be the ability to verify that the fluorescence does what it purports to do, which is to identify areas of tumor.

I don't know if that helps you put it into context. And we would invite the neurosurgeons to opine as to whether or not, in their view, this potentially could be a useful tool to their surgical practice.

DR. ROYAL: We are going to be breaking at 12:30 for lunch. But are there any other questions? Dr. Herscovitch?

DR. HERSCOVITCH: Just a comment to what Dr. Marzella says. If it's a visualization claim that it visualizes tumor, which is PPV, how do we have to take into account the NPV? Because it in lots of cases didn't visualize that tumor. So just to make that comment.

DR. MARZELLA: It's a critical component of the assessment obviously. Both PPV and NPV are important.

DR. HERSCOVITCH: So although PPV was picked retrospectively as a primary endpoint, if it's visualization, you want to know if it visualizes something that is there and if it correctly says something isn't there --

DR. MARZELLA: Exactly.

DR. HERSCOVITCH: -- in which case that's not the case, given the low NPV.

DR. MARZELLA: Yes.

DR. ROYAL: Dr. Toledano?

DR. TOLEDANO: So it's Dr. Toledano, and while we're talking about PPV and NPV, I'd like to bring up this question of biopsy level and patient

level because the outcomes happen at the patient level. The medical management happens at the patient level.

So is there a preference within FDA on patient level, biopsy level, something in between? Please discuss.

DR. MARZELLA: I'll let the statistician comment. What we are looking is basically for concordance between these outcomes, and they are very concordant. But I'll let the statistician comment on the value of all of them.

DR. MUCCI: Well, if possible, patient level. If there's a way to get patient level, it's preferable.

DR. MARZELLA: I think we would all agree that that's the most stringent, and that was the one that the performance was lower relative to the outcome.

DR. MUCCI: I can give a general kind of example. A patient-level outcome that would be determined by something you find locally, you look under, say, a control, you see all you can find.

And then a patient-level outcome would be, with the test diagnostic, do you find something you didn't find with the control?

It'd be that one extra thing you find on the patient. That would be a patient-level outcome.

DR. TOLEDANO: So its Toledano again, and I'll just continue. Is there a way, when you're looking at these biopsy levels, to not be so stringent, all the biopsies have to be positive, but to do some sort of a clustering?

Like you looked at averaging, and you said let's look within each patient. So let's go to slide 14. Definition 2 says, let's look for each subject. Let's take the percent of fluorescent biopsies that are histology positive, and we get for each patient that percent, and then we average across them.

An additional option would be something like methods to analyze clustered binary data like a good old Rao and Scott. So you put each biopsy in, but you adjust for clustering of the biopsies within a patient. I just wonder if that's an

approach that you have considered or would consider.

DR. MUCCI: With the one that was used, the biopsy level -- I don't know if I'm answering your question -- the biopsy level, if you were going to get confidence intervals of any kind, you would have to take clustering into account.

DR. TOLEDANO: They didn't.

DR. MUCCI: Then I guess not, yes. And I would mention that the easy way out with within-subject is that you're treating each subject. You've got an ID, so the clustering drops out of the picture.

DR. ROYAL: Dr. Jacobs? This will be the last question.

DR. JACOBS: The last question, okay. It's again another philosophical question. Given that this is an often indication and pretty deadly disease, what weighting would the FDA think that we should be providing to those aspects?

It's much harder obviously to do a large clinical trial or to do controlled clinical trials

with diseases where there aren't very many patients or they present with awful symptoms.

So what's the balance there? Because this is obviously not hypertension. Then this is something where you're providing a little extra information to a surgeon who then uses it according to his or her judgment.

So is there a feeling of how we should look at these?

DR. MARZELLA: Yes. I think that it would fall under their risk-benefit calculation. So given the lethality of the disease, given the fact that there isn't a satisfactory alternative, what would be the risk-benefit?

So we would accept a small increment in benefit if it was outweighed by the risk. But by law, we are required to have evidence that a drug is safe and effective. So we would not market something that we did not have evidence. We would not have substantial evidence for efficacy.

So it's a risk-benefit calculation. If there were serious downsides to this drug, we would

be requiring more data to fully evaluate the safety. This is a hypothetical. So it's largely a risk-benefit consideration.

DR. ROYAL: Dr. Frank, you have the last question.

DR. FRANK: Thank you. It seems to be clear from Dr. Brennan's presentation earlier of the clinical science here that resecting at least 80 percent is important for patient benefit, and resecting more is better.

It further seems to me that we've seen evidence that the fluorescent agent identifies tumor that was missed on typical white-light visualization. And therefore, that could only help the surgeon in the use of his or her clinical judgment as to whether go further, balancing that against the risk of diminishing function. However, it does seem to me to be of potential concern if the fluorescent agent were leading the surgeon inappropriately to remove tissue that shouldn't have been.

So my question for Dr. Ballard and/or

Dr. Marzella is, is there any concern that this agent might lead a surgeon astray to resect tissue that needn't have been resected?

DR. MARZELLA: Maybe I'll begin by saying we are placing reliance on the randomized clinical trial to have a comparison of adverse neurologic reaction. As it was pointed out by Dr. Ballard, there is some suggestion that perhaps at least some of the serious neurologic events are higher in the treated arm relative to the control.

So there is that risk-benefit consideration. However, having said that, I think that the FDA assessment at this point is that safety profile seems to be acceptable given the setting in which the drug is going to be used.

DR. BALLARD: I just want to say, if you look at the data that was presented -- I think Dr. Mucci had one of the slides -- a number of false-positive results in this study were very, very low. So I think the likelihood that it's going to lead a surgeon astray in that regard is probably not very real.

A lot of this, because of the area that you're operating in, so much relies on surgeon's judgment and surgeon's ability to identify areas that are critical. And they're not going to take it out even if there's fluorescence.

DR. ROYAL: We will now break for lunch. We will reconvene again in this room 45 minutes from now at 1:15 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember there is no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:34 p.m., a lunch recess was taken.)

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

(1:16 p.m.)

Open Public Hearing

DR. ROYAL: I am going to resume the meeting.

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 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 statements, to advise the committee of any financial relationship that you may have with any industry group, its products, and if known, its direct competitors.

For example, this financial information may include the industry's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

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

Will speaker 1 step up to the podium and introduce yourself? Please state your name and any

organization that you are representing for the record.

DR. ZUCKER: My name is Lloyd Zucker. I am a neurosurgeon. I am a surgical consultant for NXDC, not paid as a surgical consultant. And I am chief of neurosurgery at Delray Medical Center, Delray Beach, Florida. I also am one of the surgeons trained by Dr. Hadjipanayis in the use of 5-ALA.

Thank you to the committee for allowing me to speak today. I'm coming to speak to you as the chief of neurosurgery from a 500-bed community hospital located in Florida. My practice covers the full breadth of neurosurgery, both cranial and spinal.

Over the past 30 or so years, I've had the privilege of caring for many patients with malignant gliomas. Unfortunately, this also translates into the fact that I've seen the passage of many patients that have malignant gliomas.

Over the 30 years, there have been many different treatment paradigms that have been

introduced. There have been methods to increase the accuracy of our resection. You have heard about some of them today, the stereotactic surgery, which certainly has changed the breadth of what we can do. But as you have heard, once the skull, the calvarium, is opened, the accuracy certainly does drop off. In fact, as I teach residents, over-dependence on what are basically virtual realities and not real-time realities can be deleterious to the patient.

There are other surgical adjuncts that you've heard about. Intraoperative MRI is certainly one of them. The expense associated with intraoperative MRI has meant that many centers do not have access to it. I'm fortunate. I do have access to it.

However, I will tell you that, even with access to an intraoperative MRI, it is cumbersome, it breaks down workflow, and has not proven to be a real-time benefit to surgery for gliomas.

The surgical judgment of the surgeon is paramount. The ability to discriminate tumor

tissue from normal brain tissue certainly is something that you've heard about many times already today. However, it would be dishonest for me to say to you that there were not times that I thought I was done only to find on a post-operative MRI that there was more that I could do.

The goal of doing what you've heard, a gross total resection or a maximal safe resection, is elusive. The ability to do it in areas of the brain, where I think you've heard, it's easier to resect more such as the right frontal area is certainly possible. But as you get to areas that are more eloquent or areas that are deeper, if you don't have a real-time way of assessing this, then you're basically lost.

I've watched over the years the development of fluorescent-guided technologies with my colleagues over in Europe. And basically, I see now that there is a scalable approachable way to access lesions that I don't have at the present point in time.

The other methods that are out there

unintentionally create barriers, so neurosurgeons, and especially the community neurosurgeons, can't provide the level of care to patients that they'd like to be able to provide.

Fluorescent-guided surgery doesn't have those barriers. Neurosurgeons, whether they are academic or in community practice, can all access the level of technology and provide the best of care.

Basically, so I stay within my time limit, I think that I'm looking at a moment where I can substantially change how I practice and the care I provide to patients that I never had the chance to before. And the committee has a choice and a chance to approve something that will assist all neurosurgeons, and I thank you for your time.

DR. ROYAL: Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. MUSELLA: Hi. My name is Al Musella. I'm the president of the Musella Foundation for

Brain Tumor Research and Information, Incorporated. Our mission is to speed up the search for the cure for brain tumors and help patients through the journey.

We run the oldest and one of the largest online communities for brain tumor patients and their families. And we have funded over 95 brain tumor research projects. We have given out over $3 million through our co-payment assistance program to help get access to the treatments they need.

I have been helping brain tumor patients through their battles for 25 years, and I lost two family members to glioblastomas. I have no relevant financial or non-financial relationships to disclose. I paid for my own travel and accommodations to come here today.

I'm here today as a brain tumor advocate to ask that you please approve 5-ALA for these people. I understand that 5-ALA has been used by over 58,000 patients worldwide and is approved in 40 countries.

Think about that number, 58,000 times, a neurosurgeon said they want to use 5-ALA on their patient for the brain tumor operation. That's a huge vote of confidence in the utility and risk-benefit ratio of 5-ALA. That's something that the American neurosurgeons can't do.

These neurosurgeons know that they have a better chance at a gross total resection when they're using 5-ALA. The importance of a gross total resection is becoming much more important now that we are close to getting a few of the vaccines approved. In the brain tumor vaccine trials, early results show a much better outcome for patients with a gross total resection.

I am in contact with many brain tumor patients every day. They are facing a horrendous battle and need every bit of help possible. I listened to the discussion this morning. If I had to make the decision for myself or a family member, I would definitely choose to use 5-ALA if possible.

When you're making your decision, think of it the same way. This is not an academic exercise

to see how we can make the evidence as perfect as possible. Lives are at stake. Base your decision on if you or a family member needed to use this drug, would you want to have it available, yes or no? Thank you for allowing me to express my views on the subject.

DR. ROYAL: Will speaker number 3 step up to the podium and introduce yourself? Please state your name and organization that you are representing for the record.

DR. WIDHALM: Yes. My name is Georg Widhalm. I'm a neurosurgeon, and I'm the chair of Austrian neurosurgery tumor section. I'm working at the medical university in Vienna, and I'm currently doing a research project in San Francisco. And I want to tell you shortly about my experience with visualization of common brain tumors with 5-ALA. So that's the university in Vienna, and I have no financial relationship with the company.

We've heard that different brain tumors can be distinguished, and the most common primary brain

tumors are gliomas and meningiomas. At the Medical University of Vienna, we've performed these procedures since 2007. And therefore, we have large experience with such procedures, approximately 1 to 2 procedures per day.

So we have heard already in high-grade gliomas, the drawback is an insufficient interpretive visualization of tumor tissue, and thus leading to an incomplete resection in up to 80 percent of cases.

That's in too big a case of a malignant glioma resection. Also for an experienced neurosurgeon, it is very difficult to localize the tumor. If you switch to the fluorescence, you can precisely localize this tumor and resect it.

In a recent study, it was shown that the high positive predictive value of 5-ALA fluorescence for detection of tumor tissue is present in high-grade gliomas. This is a typical image after assumed complete resection. The neurosurgeon thinks the tumor is resected, and if you switch to the fluorescence slide, you see this

typically fluorescent what I really very often observe in such resections, so it's a big help for us.

What about low-grade gliomas? They are characterized by intratumoral heterogeneity. So the surgical drawback is an insufficient interpretive identification of potential areas with focal malignant transformation. Thus, it might lead to histopathologically under-grading and thus incorrect diagnosis and treatment failure.

Therefore, a sampling from the metabolic PET hotspot is recommended. However, small hotspots cannot be found because of the brain shift. So we thought also to administer 5-ALA in suspected low-grade gliomas and found in such low-grade gliomas or suspected low-grade gliomas that a focal fluorescence correlates with malignant histology, areas of metabolic activity, increased proliferation rate, and also the criteria of anaplasia.

That's a typical case of suspected low-grade glioma. What we did with 5-ALA and outside the PET

hotspot, we found no fluorescence and only low-grade tumor tissue. And inside the PET hotspot, we found a really bright fluorescence. And this was already malignant tissue with a high proliferation rate. And only because of this fluorescence sample, the tumor was created as an anaplastic glioma and received the required therapy. So it was really very helpful in this case.

I also want to come to meningiomas. We found in a large study that also visible fluorescence is present in over 90 percent of cases, so it's also a market for interpretive visualization of meningioma tissue. We also can identify bone infiltration and also satellite lesions that are near the tumor and can lead to local recurrence.

So to conclude, in high-grade gliomas, 5-ALA fluorescence is able to visualize tumor tissue with a very high positive predictive value to maximize the tumor resection. In suspected low-grade gliomas, 5-ALA is able to detect intratumoral areas with malignant transformation to enable a precise

diagnosis and adequate therapy.

In meningiomas, the 5-ALA fluorescence is able to visualize residual meningioma tissue to reduce the risk of local recurrence. Thank you.

DR. ROYAL: Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. KEENAN GILIBERTO: My name is Jennifer Keenan Giliberto of Atlanta, Georgia, and I have no financial ties to the applicant. I stand before you as a brain cancer patient with countless patients and families looking for hope.

Aside from death and taxes, there are few guarantees in life. Each of us makes decisions weighted by risk and reward, and some of us approach it with a measured conservative tact, while others simply take a leap of faith, jump first, and ask questions later. As homage to YOLO, you only live once, yet we take and accept that life is riddled with risk and we collectively relish, publicly or privately, in what taking a

chance means and how each of our lives can be impacted.

Ten years ago, at 32, I left a neurosurgeon's office and privately resolved against the grain of grim statistics that I would live to turn 40. Nine years ago, I consented to have a portion of my scalp shaved, skull cut open, and a portion of my brain removed with my brain tumor.

In the weeks, months and years that followed, I was encouraged to trust in the process, live life, and embrace the reality that while statistics exist, they cannot define you.

Our lives have been impacted immeasurably, and we have struggled and grown as families and individuals. We've rode an emotional rollercoaster with frustration at the lack of hope offered in medical treatments and have resolved to steadfastly make this journey matter on our own terms. We're focused and grateful and have gained perspective.

At 42, I watch as the little boy who began kindergarten the week prior to my craniotomy

prepares to begin high school and stands before you today. We have welcomed a third child, and we have chosen to embrace courage, perspective, and hope rather than fear.

Yet, we await medical advancements and we still live our lives in segmented 12-week periods of time between my MRIs and oncology appointments. The process of being a patient, living in a compartmentalized life in between scans and the in-your-face reality of the toll it takes is difficult.

I refuse to accept that I simply have an orphan cancer and my treatment plan has remained unchanged for decades. I refuse to accept that life expectancy for brain cancer patients is measured in months, and I'm simply a statistical outlier. I refuse to accept that surgical margins are determined by estimates when surgical precision is available with 5-ALA.

Your affirmative recommendation of 5-ALA would provide me and every patient in our families a meaningful, precise visual surgical tool that

would give us hope. There is yet to be a surgical advancement as significant as 5-ALA that would move the ball forward at the surgical outset, and impact patient outcomes, and allow for a more targeted, impactful, post-surgical treatment regimen.

This is an advancement that matters, gives me hope, and makes living in the shadow of a recurrence much more palatable. I respectfully ask that you give us a chance and acknowledge that the benefits of 5-ALA most certainly outweigh the minimal risks.

As a documentary photographer, I worked for 20 months following a GBM patient from his tumor resection in March 2015 to his death on November 6th of 2016. It's important to note that he did not have a recurrence of his GBM. Rather, he was diagnosed with a secondary cancer, leptomeningeal carcinoma.

Josh was a participant in the clinical trial for 5-ALA and I was present in the OR during his surgery, where I witnessed how precise and clear the tumor was visible and how abundantly important

the visual tool was to Dr. Hadjipanayis. To quote Albert Einstein, "If you can't explain it simply, you don't understand it well enough."

I'll now leave you with a brief slide show from my documentary and images that transparently represent the totality of the brain cancer experience.

(Slideshow played.)

DR. KEENAN GILIBERTO: Thank you for your time.

DR. ROYAL: Will speaker number 5 please step up to the podium and please state your name and organization that you represent?

MR. GILIBERTO: My name is Tucker Avery Giliberto from Atlanta, Georgia, and I have no financial ties to the applicant. I have a few memories before brain cancer, fundraising, advocacy, courage, and fear became woven into the fabric of our lives.

My parents have been very open with my siblings and me about what my mother's diagnosis is. The magnitude of it will affect her life and

likelihood may end her life. That has not been easy on me or my mother.

My mom has brain cancer. I know what it is like for her to have MRIs every three months because, as a family, we all share in the anxiety. We talk about it, but it is hard. Our normal is not most families' normal. It would devastate me, my siblings, and my father if her brain tumor grew back aggressively. I know you understand what that would mean.

However, there is now 5-ALA, a valuable visual surgical tool that could make the process of getting rid of her brain tumor more precise. I ask you to consider 5-ALA available to my mom, what that would mean to me and other family members of a brain cancer patient.

There is little about a cancer diagnosis that leaves a patient or family feeling they have control. I believe that 5-ALA would provide my mom and our family a level of control. Rather than hoping a surgeon estimates margins correctly, we could have the confidence that an entire malignant

tumor was visible. Simply having the knowledge of such a precise surgical tool would ease the stress and enable a more effective and targeted treatment plan.

I would do anything to help my mom, and I know you would do the same for your own mother. It has been very hard to have mom with a brain tumor. As much as her life has been immeasurably changed, so has mine. I wish her cancer had never happened in the first place. However, you have the ability to advance the ball and give my mom and other patients a better chance to live, thrive, and survive with 5-ALA.

I often hear my mom referred to as humble, brave, inspiring, and fearless, and she is all those things and more. But to me, she is my mom. So I stand here today at 14 and ask you to think about if your mom had brain cancer and consider how 5-ALA could alter the course of her treatment and benefit the quality of her life. Would you not want that for her? Thank you.

DR. ROYAL: Will speaker number 6 step up to

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

DR. KALKANIS: Those are some very tough acts to follow.

Good afternoon, everyone. It's an honor to be here with you. My name is Steve Kalkanis. I'm the chair of neurosurgery at Henry Ford in Detroit, where I also direct our cancer institute, and I'm chair of the section on tumors for the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. I have no financial ties to the sponsor.

I'm here today to tell you about my personal experience with 5-ALA, using it in the operating room. At my institution, we have every imaginable surgical innovation available to us. And even with that, 5-ALA stands above, way above, all of the rest in terms of providing me and my co-surgeons with a real-time tool to make a difference for resection, and we believe for life expectancy for our patients.

This is a case that I feel is indicative of what a broad indication and approval for 5-ALA would bring. This is a patient who developed actually a low-grade glioma in 2008. There was a recurrence. We weren't sure what it was. We assumed it may be high grade. In fact, it was. On biopsy, it had an extremely high malignancy index.

We took the patient to the operating room, and using our surgical armamentarium completed the resection. We thought we were finished. This is one of the first cases we used 5-ALA on, and I'll show you a video now of what it looked like.

This was when we were done with the resection. We switched to the blue light. We examined the depths of the tumor resection cavity. And to our surprise, we found immediately this pink fluorescence that was coming through the bottom of the resection. This is tumor that would have been left behind. Again, we thought we were finished.

We then resected it and got a scan that looked like this, removing essentially almost 100 percent of the contrast-enhancing tumor, and

based on all available evidence known to the glioma literature, significantly impacting this patient's survival.

Here's another video of a case in which we actually used our intraoperative MRI. The intraoperative MRI suggested we had gotten all of the tumor out, but when we used the 5-ALA, you see here all of the fluorescence that is poking up at the margins that could not even be detected by the intraoperative MRI.

This was very significant to us because we typically rely on the intraoperative MRI. This is a very expensive tool that is only available at a few centers in major academic centers around the country. But this real-time agent allowed us, as we were operating on the patient, to understand that, in fact, there were infiltrating cells left behind.

Again, I can't emphasize enough as a surgeon what it means to be able to visualize these invading cells when you think you've done your absolute best for the patient, knowing that there's

an additional tool that we could have in our armamentarium to make the resection more complete.

I should add that anyone who's familiar with the glioma problem understands that you're always going to get lingering, invasive, infiltrative cells, even on the other side of the brain sometimes. So it's not clinically relevant for us if some of those histologically positive cells don't fluoresce.

What's relevant for us is that the cells that do fluoresce act as a road map to allow for safer resection. We're not going to simply follow the fluorescence if it's not in a safe part of the brain. The surgeon, at the end of the day, makes that final determination based on his or her experience, and the mapping tools, and the functional navigation that we have. But if we had a tool to understand that there's a few cells left over and we knew exactly where they were, we really feel we could make a significant difference for these patients.

In summary, we use an intraoperative MRI all

the time, but 5-ALA is real time, and it certainly would be much more widely available and accessible to surgeons and patients across the country. The feedback that it provides is based on actual tumor physiology, and the tumor differentiation is made significantly easier.

It's been very well tolerated by all of the subjects that have undergone this testing at our institution, and we feel that it significantly adds in the treatment of this disease.

I would add that as the president of the Neurosurgical Oncology Association, the tumor section with over 2,000 members around the world, we constantly address the need for clinical trials to improve the outcomes for brain tumors. All of the members of our executive team on this section on tumors strongly support this initiative and this process. And I thank you for your time today.

DR. ROYAL: Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. SHAFFER: Yes. Good afternoon. My name is Geri-Dee Shaffer. I am involved with the Southeastern Brain Tumor Foundation. It is a 501(c)(3) not-for-profit organization and a public charity. We're located down in the Atlanta, Georgia area. I have no financial ties to the applicant who is here today, at today's meeting. Sorry.

I actually am here today to speak on behalf of numerous people who I serve, and people who have impacted my life, and people who continue to impact my life on a daily basis.

Since 2012, I have served at the pleasure of the board of directors for the Southeastern Brain Tumor Foundation. My current role at the SBTF is in the capacity of executive director.

As I stand before you today, I am not just here as a brain tumor advocate. I'm here as a voice for the glioma patient, for those who are living with the disease and for those who have departed this world as a result of the disease.

For 31 years of my life, I worked for a

medical device company, and I retired back in 2011. During my career in med device, I witnessed the development and the FDA approval of new medical devices. Some of the devices were specifically used in brain surgery.

What I didn't fully realize during those 31 years in med device was the hope which these FDA approvals brought and provided to patients. I've been with the foundation here, the Southeastern Brain Tumor Foundation, for four and a half years now, and my eyes have been opened to the significance of the medical advances that are being made. But they've also been opened to the need to expedite the approval of these medical advancements. And I've also had my eyes open to hope, which comes with the words "FDA approved."

In addition to heightened realization of the impact associated with the words "FDA approval," I've also experienced great sadness in the last four and a half years, in particular the death of 11 people in an 11-month period of time, and all of these people were diagnosed with a glioblastoma. A

piece of me actually has been taken away with each of them, so I'm very passionate about what we're talking about here today.

Through my work at the foundation, our brain tumor support group patients have shared stories. Some of them have traveled throughout the U.S. in search of better surgical options. Some have actually traveled internationally and obtained surgical options.

I've also heard from our patients and our constituents about confusion to understand why certain surgical techniques and technologies are available abroad but are not available here in the United States of America, where we are the most powerful and advanced nation in the world.

I've also listened to stories about initial surgery, which didn't completely excise a tumor. People tell me they're still living with this piece of whatever. I've also heard about complications of surgery which led to neurological deficits. I've heard about frustrations at local-area hospitals that lacked high-tech tools like

intraoperative MRIs and patients had to be sent somewhere else.

In my opinion, 5-ALA can provide hope for brain-tumor patients with resection of more tissue with the potential of increased survival rates, and these accomplishments can be achieved without the high-tech tools like intraoperative MRIs.

The imaging agent 5-ALA provides real-time detection and full visualization of malignant tissue during glioma surgery. It represents a technological advancement, something which I have not heard about or seen in a long time. We're hoping for a win here, a win like a post-op conversation with a neurosurgeon that says something like, "We excised the entire tumor," something like, "There were no complications," and something like, "We don't think secondary surgery will be needed."

It's my personal hope that the decisions of the committee will provide brain-tumor patients the possibility of better surgical outcomes. It's my personal hope that the decisions of this committee

will provide brain-tumor patients a financial reprieve by an approval which results in insurance coverage for surgical procedures. And it's my personal hope that the decisions of the committee will not deny these brain-tumor patients the possibility of extending their life expectancy.

In my opinion, 5-ALA represents forward progress, which our brain-tumor constituents dream about. Thank you for your time. Thank you for allowing me to share this opinion.

DR. ROYAL: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. Before we move on to the next part of the meeting, the sponsor had a slide that they wanted to show us. I believe this is the slide that did not project properly the first time.

DR. STUMMER: Slide up, please. So again, I apologize for the technical problems with this slide. We were talking about the issue of completeness of tumor resection as related to event-free survival and the course of the NIH after

surgery.

So this is what this slide actually summarizes. Patients are stratified. These are the complete patients from study 3. We stratified according to extent of resection, and what you can see here is event-free survival where an event is deterioration of the NIH Stroke Score in the face of stable or increased steroids.

As you can see, the patients that have had complete resections, where we might intuitively be worried about a negative impact on neurological function, they actually did better and remained more stable over time. That was the point I wanted to make with this slide. Thank you for your understanding.

DR. HADJIPANAYIS: Thank you, Dr. Stummer, for clarification of PFS. Committee members and FDA members, 5-ALA does provide real-time visualization of tumor tissue that delineates malignant tumor tissue.

It's unquestionable the amount of tumor tissue that we visualize in addition to white

light. This is a tool that's additive to our current armamentarium as neurosurgeons. Not only will it help us neurosurgeons resect more tumor tissue, but it will help our patients with better patient benefit, as you heard in the randomized phase 3 study doubling of the extent of resection, and also fewer repeat surgeries.

This is a universally fatal disease. We need all the help we can get here, and I think we've heard from our patients and family members of the importance of this today.

Questions to the Committee and Discussion

DR. ROYAL: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. We would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So the questions that we've been asked to discuss, I'm going to read. Discuss the efficacy outcomes used in this drug development program and their acceptability for substantiating the proposed claim. In your discussion, please consider each of the following points.

The applicant presented data demonstrating the intraoperative visualization of malignant tissue with calculation of the percentage of visualized tissue fluorescence, verified by histopathology, the positive predictive value or PPV.

Please discuss the clinical significance of the provided PPV measurement of malignant tissue visualization with the use of 5-ALA and whether the provided data on malignant tissue visualization are sufficient for establishing the efficacy of 5-ALA.

If committee members would like to speak, if you turn up your name card, that would be helpful, thank you. Dr. Hackney?

DR. HACKNEY: So I think the positive predictive value is useful in that it would suggest

the surgeon is not going to end up resecting normal tissue or tissue that's not densely infiltrated by tumor by using the guidance of 5-ALA, and that's what that metric can tell us usefully in this context and as they proposed to use it. Targeting those areas that are fluorescent typically targets those areas of high tumor density, and I think that's an appropriate measure.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: I also think it's an appropriate measure. I think that providing information to a surgeon, who will then use that information with their own clinical judgment and their surgical judgment to decide whether or not to resect any areas that they see of high fluorescence, I believe that they will normally proceed with their white-light resection first because it's a lot easier to see anything in white light, and then move on to the fluorescence.

So I believe that this is additive, but that the information itself may or may not change what is done by the surgeon.

DR. ROYAL: Any other comments? So I'll summarize what I've heard. Dr. Toledano?

DR. TOLEDANO: So this is Toledano. I was a little slow to flip my card. I agree that PPV is a useful measure. I agree with Dr. Jacobs that the surgeon then takes the action appropriate in the context of what's happening in the brain. But we can't just rely on the PPV, so I would like people also to bear in mind the negative predictive values or what happens with things that don't fluoresce.

DR. ROYAL: Dr. Roberts?

DR. ROBERTS: I agree again with the other speakers that PPV is an important predictive value, but I think other things are important, too, such as looking at the tissue that fluoresces, but is actually negative for tumor.

Those numbers are low here, but I think that it's important to take into account that we're not resecting normal tissue inadvertently. And I think another thing that's important to look at this was the extent of resection and the correlation with the extent of resection afterwards.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: I agree with what the other folks have said about the very good positive predictive value, and it does what it says, and it does point out areas of tumor that would not be visualized by white light.

The negative predictive value was not very good, not being able to visualize more of the tumors, so the drug isn't perhaps doing as well as one might have hoped. But still, the glass is half-full.

But I think it would be important for neurosurgeons as part of the training process to really have an understanding of the fact that there are going to be areas with tumor that don't fluoresce.

Of course, the whole thing has to be assessed under the umbrella of no matter how good or careful the surgeon is and the fact that the MRI contrast post-op can very well be negative, of course, just by the nature of the disease, as we've all heard, there still will be infiltrating tumor

somewhere at the margin. So we can't expect perfection, but at least some advancement towards improvement.

DR. ROYAL: Dr. Byrne?

DR. BYRNE: I agree that the positive predictive value is an appropriate measure, and I would particularly point out the actionable portion of the fluorescence, the strongest portion of the fluorescence, will be the most actionable part of the operation for any surgeon, and that correlates very strongly with dense cellularity of tumor. And the weaker portions of fluorescence, as we saw examples here, are going to be a judgment call of the surgeon based on safety.

DR. ROYAL: Dr. Zamorano?

DR. ZAMORANO: Yes. Basically, I agree with everything that has been commented. In terms of opinion, I think the data, we have demonstrated a usefulness of this 5-ALA as an adjuvant to the interpretive visualization of malignant tissue in brain surgeries.

Any approval would have to be with a lot of

concern with what we have discussed in terms of the false negative and false positive and certainly is something that cannot be used as the only way to interpretive visualize or plot a surgery.

So in terms of the objective, of the support to add something to our armamentarium as a neurosurgeon, I am very positive about that, but at the same time, we need to be careful that this can give a false impression of what really we can achieve here.

So as an adjuvant for interpretive visualization, to be used with all of our other tools, I think it could have a very positive part in the armamentarium. Also considering that most places do not have actually interpretive MRI, this could be a very important adjuvant to the surgery than with a pre-operative-acquired MRI -- that most neurosurgeons perform this surgery nowadays. So this would be additional information that could be very useful.

DR. ROYAL: Dr. Frank?

DR. FRANK: I think taking together the

clinical evidence showing the beneficial effect of the larger extent of resection, taking that together with the intraoperative MRI data on the rare occasions when it's available, showing that 50 percent of the time, the patient has to go back for additional resection, creates a clinical imperative for something like this, and PPV is the appropriate parameter. I think NPV is confounded by the infiltrative nature of the disease.

DR. ROYAL: If there are no other comments, it sounds like there's fairly good agreement among the committee that the PPV measurement is a useful measure to establish the efficacy of 5-ALA. There's some concern about the false negatives, but again, when we're dealing with an infiltrative process, that's going to be expected.

If we can move on to part B, please discuss the potential clinical importance of finding non-fluorescent tissue samples being also positive for malignancy in histopathology. So we've discussed this a little bit in terms of the false negatives.

Anyone want to make any additional comments

about the false negative results? Dr. Gilbert?

DR. GILBERT: So I think this gets back to the question of the 5-ALA clearly increasing the likelihood of what we would define as a complete resection, recognizing that it's an imaging definition and may speak to the fact that the 5-ALA will be best, or delivered best to the area of the tumor where the blood-brain barrier has been impaired, which would be the same area that receives the contrast.

So you are in fact getting a visualization of the area that was contrast enhancing; hence, I think the close correlation. So in that context, I think it does what it has set out to do, which is identify that area.

I think from a surgical resection standpoint, that's typically the area that is safest to resect. So it does not effectively unfortunately address the area of tumor that is in the area where we don't recognize it as anything other than by imaging the T-2 FLAIR abnormality most commonly.

If it picked up that area in high concentration, I think the extent of resection from a biologic standpoint would be higher. But for what it has done, I think the PPV, as we talked about, suggests that we're getting a high concentration of cancer cells removed, that there's, in some situations, as our neurosurgical colleagues have shown us, incremental and beneficial, but doesn't get us to the next level, which would be the non-fluorescent tumor cells.

So that means that this is an adjunct, but will not take us to the next level of tumor burden reduction. And I think we need to recognize that this happens to a degree.

The data that they showed us from the combination of the studies, it's about 15 percent of the time there is residual tumor that has a high density, that for whatever reason has not reached blood brain barrier adequately to get the 5-ALA in concentrations high enough to be visualized. But for the most part, the tumor that is left behind is the infiltrative tumor that is intercalated amongst

normal brain and oftentimes wouldn't be resected because of the concerns of neurologic injury.

DR. ROYAL: Any other comments about the false-negative rate?

(No response.)

DR. ROYAL: So again, to summarize what I heard, we know that we're going to leave behind tumor. This agent would allow you to remove more tumor, even though there's still going to be tumor left behind.

If we can move on to C, one of the efficacy outcomes used by the applicant is an improved completeness of resection, defined on the post-operative MRI enhancement.

Please discuss the clinical importance of complete resection in the setting of glioma surgery and comment on the clinical meaningfulness of using post-operative MRI to measure the completeness of resection.

Dr. Gilbert?

DR. GILBERT: So I think this was one of the critical questions. So complete resection, I think

it's appropriate to put into quotation marks. Certainly, we've all heard about the challenge of infiltrative disease, et cetera. But there is now increasing evidence that tumors in which the contrast-enhancing component has been completely removed are less likely to have a phenomenon known as pseudoprogression, where we get inflammatory change after radiation and chemotherapy, which is the standard treatment.

The importance of pseudoprogression is it's so often mistaken for true progression, and where the therapy is actually very effective is misinterpreted as being ineffective and treatment has changed inappropriately. So if you reduce the likelihood of a misdiagnosis by having a complete resection, that's a good thing.

The other area in which it is I think increasingly important is as we venture in the field, into the area of immunotherapy, when there is residual-enhancing disease, those patients are much more likely to have a substantive inflammatory response, which is good, but it's often manifest as

a mass and a lot of brain edema. And again, you wind up particularly with a clinically relevant pseudoprogression, where there's neurologic decline, often mandating a subsequent surgical procedure.

So I think going in with what we would see as a complete resection of enhancement, anything that we can do to increase that safely reduces the pseudoprogression from either chemoradiation or the potential consequence of a positive immunologic response.

DR. ROYAL: Dr. Byrne?

DR. BYRNE: I would agree with the last comment and just add that all of the recent volumetric studies done on this, understanding that they're retrospective in nature, all come down on the side that a complete resection does improve length of survival.

I'll also point out that we're not likely to see a randomized controlled trial on this going forward. Surgeons and clinicians don't feel that there's equipoise to randomize at this point.

DR. ROYAL: Other comments. Dr. Toledano?

DR. TOLEDANO: Thank you. It's Toledano. So I think we have to go with our gut in many ways on this one and go with what the surgeons are learning from their experience in these procedures.

It's very difficult to sort out how to interpret progression-free survival because it's confounded with all of the interventions that happen after surgery. So it's even hard to figure out what you would do if you knew this thing, and that thing, and the other thing, all of the things that can happen between the surgery and the prolonged survival. We're going to go for prolonged survival.

There are two subbullets, little 1 and little 2. 1 is the prescribing information. I don't think the applicant is trying to make a claim about these endpoints, so I don't know if that needs to go in. I'm ahead of you?

DR. SHEPHERD: Yes.

DR. TOLEDANO: Oh, you're still doing that one? Oh, goodness. I thought we finished that

one.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: For the comment here, on the meaningful of using post-operative MRI to measure completeness of resection, I will point back to what Dr. Gilbert said on point B, which is that it's a little bit of a circular argument because we defined the tumor initially by it having enhancement, meaning you were only looking at areas of reduced blood brain barrier. And then we later defined the complete resection by the same thing, which means that if there are areas that do not have such defective blood brain barrier -- and there may be in much of this infiltrative disease -- we wouldn't see that in any case.

So I'm not sure how relevant that is, although I understand it's what's used clinically because I think it's the only measure we have. But I think people should be careful not to decide its truth.

DR. ROYAL: Any other comments? Both of your name cards are up. I don't know if you have

another comment. Yes. Go ahead.

DR. ZAMORANO: I have a couple. Yes. My comment would be with respect to this point, that I think the studies that have been presented to us, we can say that there is an improvement in the amount of resection, tumor resection. I don't think that we can say that this is completeness of resection. Number one, we have the issue of the false positive. We have the issue of the false negative.

So to me, it would be a better assessment to state that this improved the amount of tumor volume resection, very important for all the therapies, any therapy. Obviously, this is not a therapeutic agent, but any therapy in brain tumors is dependent of the amount of tumor volume that is left after resection.

The other point that I mentioned prior that may be important is most surgery is done for malignant gliomas, not with an intraoperative MRI. Even with an intraoperative MRI, you have the problem of the brain shifting. So the use of

substance or some adjuvant to surgery helps us to increase the amount of the tumor volume is also an important factor for neurosurgeons.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: So I did really note the large increase and completeness of resection, 36 percent to 65 percent with the use of the drug. And although statistically, it was pointed out that there was some concern that there was no direct link between the PPV and completeness of resection, that study 3 was still a double-blind, randomized study, and using the drug by whatever means lead to that substantial improvement in completeness of resection.

With regard to the clinical meaningfulness of the post-operative MRI, well, that's basically what the field has. And we're not really here to discuss the limitations of post-operative MRI and not showing infiltration, but the studies that have used completeness of resection have shown that, when that occurs or very high volumetric resection, then outcomes are better.

The general concept expressed early in the FDA briefing document, that medical imaging technique by itself almost never makes the patient better, but a medical imaging technique could lead, by its results, to actions. And those actions secondarily lead to improved outcomes.

So I think this does show that it leads to completeness of resection improvement and volumetric resection improvement. And even with the limitations of MRI, when you do have MRI "completeness of resection," all those studies, even though admittedly not themselves double-blind randomized, et cetera, have the preponderance of evidence that shows completeness of resection does lead to better outcomes.

So that's how I comment on both those points.

DR. ROYAL: I don't see any other comments, so I will just summarize what I've heard. We have imperfect tools to determine the completeness of resection. As a matter of fact, we know that the resections are not complete. However, using these

imperfect tools, prognosis is better the more complete the resection is.

The other point that I think Dr. Gilbert brought up, which I thought was interesting, was leaving tumor behind, leaving gross tumor behind, complicates following the patient because you are more likely to see pseudoprogression. So the more complete the resection, not only is the prognosis better, but it helps to follow the patient subsequently.

So we're on D. In assessing the totality of evidence of the potential benefit of 5-ALA, please comment on the clinical significance, if any, of the observed improvement in progression-free survival and of the lack of improvement in overall survival.

In your discussion, please comment on the following, whether either should be mentioned in the prescribing information if 5-ALA is approved for marketing in the U.S. And the second part is how the outcome of progression-free survival could relate to potential assessment of patient-reported

outcomes, and what type of patient-reported outcomes would be relevant in this setting. Dr. Gilbert?

DR. GILBERT: So first, the progression-free survival was different. I'm always leery, as has been mentioned, about the determination of progression-free survival and what its true clinical relevance is.

I think when it has been informative, it's been in the context of patient-reported outcomes measures, so I'm actually responding to both simultaneously.

I don't think that the Karnofsky Performance Score, which is commonly used in neurooncology, is a very effective tool. It's quite insensitive to change. As a matter of fact, it is completely insensitive to things like aphasia, so patients who can't speak can still have a Karnofsky of 90. They can do everything except work, and they are actually symptomatically devastated.

So we use it. It's convenient. It's certainly widely used. So everybody knows it, but

in the context of understanding the significance of prolongation of progression-free survival, it is, I think in my view, inadequate.

So we don't have very good comprehensive functional measures, but what we have successfully used are measures of neurocognitive function and measures of symptom burden. And those looked at longitudinally would put I think a better understanding of what progression-free survival would mean in this context.

So my recommendation would be that what we have heard is that this agent helps the neurosurgeons do a more extensive resection and that it also substantially increases the likelihood that all the contrast-enhancing material on imaging will be removed. And that is quite an accomplishment, and I think the outcomes results, I would have to be a little circumspect about.

DR. ROYAL: So specifically answering this question, whether either should be mentioned in the prescribing information, you're saying that you're not in favor of mentioning any effect on

progression-free survival or overall survival?

DR. GILBERT: That is correct

DR. ROYAL: Other comments? Dr. Jacobs?

DR. JACOBS: I'm in agreement with that for the same reasons. I think in terms of progression-free survival, what may matter to the patient more than the complete resection is what it does. More complete resection may in fact lead to poorer patient-reported outcomes, depending on what you're resecting.

So I think that's a very separate thing from what we've done here. And I don't know the particular reported outcome measures that people use. I don't know what mechanisms there are. I know that they exist. But that would be a separate thing I think to explore, and in my mind does not tie to this approval or not approval.

DR. MARZELLA: We would welcome comments on that aspect because it's something that we should be looking forward to in the future, to using more frequently.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: Just very briefly, I would agree with the two previous speakers and just note that when the FDA did their analysis, the conclusion was that there was insufficient evidence for indications of improved clinical outcomes, which I think is important.

Also, with regard to the clinical outcomes, you may have a better MR at 6 months, but I think it's really important to consider this could be done down the road, patient-centered clinical outcomes that are meaningful to individual patients because they're the ones ultimately who we're trying to help.

DR. ROYAL: Dr. Toledano?

DR. TOLEDANO: Now, that little bullet point 2 at the bottom of section D, I agree with everything everybody else said. With these patient-reported outcomes, I think it is important to get ones that are meaningful to the patients and also ones that have a history, have known psychometric properties, not just somebody making something up or picking an arbitrary cut point to

say this is somebody who's doing well, this is somebody who's not doing well.

I'm so happy that FDA is interested in the patient experience and in what we can do to improve that, but we have to measure it with good tools.

DR. ROYAL: Dr. Ballard?

DR. BALLARD: [Inaudible - off mic].

DR. ROYAL: So does the committee have any comments about these --

DR. BALLARD: Right. So in reviewing the literature, there are basically two general measures for cancer patients that you're probably all familiar with, the EORTC Cancer Quality of Life Questionnaires and then the Functional Assessment of Cancer Therapy or the FACT questionnaires.

These include two sections, usually a general measures outcome patient functioning and then also disease specific. So you have the EORTC BN-20 and the FACT-Brain, which are specific for patients undergoing surgery for primary brain cancers.

They've been validated for those measures.

They've also been used for patients undergoing surgery for metastatic disease and other things, but they're not validated for that.

Next slide. The other type of things that might be something that would be worth discussing are some of the neurocognitive function assessments that are available. And this is just sort of a list of some of the ones that are commonly used, and it would be interesting to hear if anybody has any comments on the validity or whether these would be of value.

DR. ROYAL: Dr. Gilbert?

DR. GILBERT: So we have actually done a lot of work with outcomes measures and completed a large international randomized trial in newly-diagnosed glioblastoma. And it was placebo-controlled, and the experimental agent was bevacizumab, the anti-angiogenic agent.

Incorporated into this was longitudinal assessment of quality of life using the EORTC instrument with the BN-20, a symptom-burden instrument, which has been validated in the brain

tumor patient population -- it's the MD Anderson Symptom Inventory, the MDASI -- but the brain tumor module and also a neurocognitive battery, which used three of those neurocognitive assessments, because, again, it's a cooperative group trial, and that battery took about 20 minutes for an examiner.

What was interesting is, number one, it was incredibly informative, and this has been published in the New England Journal in 2014. Much to our surprise, the patients who were on the bevacizumab -- again, everybody was blinded -- had a decrease in quality of life, increased symptom burden, and worse neurocognitive function. So it was very informative.

The other thing that was really informative is that the quality-of-life instrument was the least sensitive to change. And that's because a lot of it is subject to patient interpretation of their sense of well-being rather than objective measures of what their symptoms are or certainly the objective measures of neurocognitive function.

So we, at least in the work that I do at the

NCI, we're shifting away a bit from the conventional health-related quality of life and more into what we consider to be more quantitative measures of symptom burden, certainly, neurocognitive testing. And we're now working on trying to come up with functional measures and are just parenthetically taking advantage of some of the advances.

The Fitbit technology can actually be adapted, and you can get real-time measures of patient function. So we're trying to do all of that to try to come up with real measures that are not subject to -- the shift in patients' interpretation of their disease as it impacts quality of life.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: I agree with Dr. Gilbert. I think these are both important, particularly in the sense of how the patient is actually doing. I would comment that if the FDA does proceed with approving this drug, I would probably not require the company to do this as a condition, as a

postmarketing condition, but I would encourage them to.

DR. ROYAL: Any other comments?

Dr. Toledano?

DR. TOLEDANO: So as a statistician, I love data. I love it all to be objective. But as a patient, I understand that different symptoms have different burden for different people. There are some things that -- if I had a cognitive decline, I would not be able to deal with that. That's how I make my living. If I couldn't make a three-point jump shot in basketball, which I've never been able to make in the first place, -- I'm not Michael Jordan.

So the emotional impact of different symptoms on different people, I think I'd like to keep as part of the picture, not just set it aside.

DR. ROYAL: So to summarize, I think the committee was in agreement that we shouldn't mention progression-free survival and overall survival in the prescribing information and was also in agreement that some efforts should be made

to collect patient-reported outcomes, that the company should be encouraged to do this, but not be required to do this.

Question number 2, discuss the possible risks associated with increased resection, that is, the potential for increased neurologic deficit. Please discuss any other safety concerns you might have about this drug.

DR. BYRNE: I would say that there is probably not much in the way of risk in removing the bright red portion of the tumor, the core. Going off into the pink area, where there may be live neurologic tracts that are still working may bring some risk.

That's the judgment part that you have heard several times today. It's all about the judgment of where are you going, what can do you do safely. That's where you can add intraoperative monitoring, awake surgery, cortical stimulation, mapping, incorporate pre-operative imaging, et cetera.

So I think that there are potentially some risks to going astray in some of the mild positive

areas, but I think just educating surgeons about that -- they're used to that. That's the same issue under white light. It's exactly the same issue. This is just one more thing that you can use.

But I'll also point out that there is literature. Ivan Ciric and others have written about the dangers of underoperating in high-grade glioma. If you do a small subtotal resection, you're much more likely to end up going back on that person early because they've got some bleeding, they've got some swelling now, and they still have retained tumor, and you're going to end up having to go back early.

DR. ROYAL: Dr. Hackney?

DR. HACKNEY: I would agree with everything that was just said, particularly the point that the issue of the risk of causing a deficit because of resection is exactly the same thing that's what the neurosurgeon thinks about before they go into the OR and the entire time they're there.

This doesn't create any new risks. This

just gives them a little more guidance when they're in there. So I think it's worth discussing, but I don't think it increases the risk.

DR. ROYAL: Dr. Roberts?

DR. ROBERTS: This is kind of getting into the next question, but I think, as far as this risk, I think it's important not to use statements such as, "This agent will delineate tumor from normal brain," because I don't think it's a clear-cut boundary between tumor and normal brain. It's a mixture of both.

Just because there's tumor there doesn't mean there's normal brain there, and we still have to, as everyone else has mentioned, use all these other things such as our determination about functional areas. So I think it's important not to have that statement.

DR. ROYAL: Dr. Gilbert?

DR. GILBERT: I would add to that, the concern about the disparity between the resections with the 5-ALA that occurred in non-eloquent versus eloquent brain, and as has already been mentioned,

this gradation of red to pink sounds like -- and again, we don't have that type of granular data, but it sounds like in eloquent areas, that's particularly risky and would hope that that would be emphasized in the training because the rate of neurologic harm was actually much higher in that setting.

But again, it's a tool. And as our neurosurgical colleagues have said, it's a tool to be used in addition to other navigation devices so that it's not a substitute. It's an additive. And that would be the one concern, that if people interpret this as, if it's red, it's okay, if it's pink, it's probably okay, and we can take some shortcuts and not do due diligence, that would be the only concern.

Again, we can't mandate that, but certainly our colleagues can very strongly encourage that the appropriate same surgical principles apply.

DR. ROYAL: I don't see any other comments. We'll move on to question 3.

Jennifer was reminding me we're going to

skip the afternoon break since this is the last important question.

The question is, do you recommend the approval of 5-ALA for the proposed indication as an imaging agent to facilitate the real-time detection and visualization of malignant tissue during glioma surgery?

So does anyone have any questions about how we vote?

DR. GILBERT: Is it yes or no?

(Laughter.)

DR. GILBERT: Okay. Is this a trick question?

DR. HERSCOVITCH: Just go over the technology.

DR. ROYAL: So about the wording of this question, do you have any questions about how this question is worded?

(No response.)

DR. ROYAL: If there is no further discussion on this question, we will now begin the voting process.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

So it's time to vote, so you can vote.

(Vote taken.)

DR. SHEPHERD: For the record, the vote is 11 yes, zero no, zero abstain, zero no voting.

DR. ROYAL: Now that we know that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

So why don't we start with -- it's only voting members. Dr. Zamorano, state your name, your vote, and if you want to, state the reason why you voted the way you did.

DR. ZAMORANO: Lucia Zamorano. I voted yes.

And the reason is because there is enough evidence that this agent is an adjuvant to the surgical procedure and can facilitate the real-time detection and visualization of malignant tissue in glioma surgery.

Still, I think it is very important to put all these other warnings that we have been discussing about false positive, false negative, judgment during surgery, and the fact that we do not have evidence that this will increase really survival of patients. But with all these warnings, I think it's an important addition to our armamentarium as a surgeon.

DR. ROYAL: Dr. Byrne?

DR. BYRNE: Rich Byrne. I voted yes. I believe that the data presented supports the approval for the proposed indication as written.

MS. ARKUS: Bonnie Arkus. I voted yes as I believe the surgeon needs this tool to provide the best care for this patient.

MS. ALMGREN: Peggy Almgren. I voted yes, as I feel this can aid the surgeon in reducing

tumor load, and it seems to be easily tolerated.

DR. ROBERTS: Donna Roberts. I voted yes. I participated as a neuroradiologist in intraoperative MRI scans, and I know the extensive involvement in those procedures, although the information that you gain from that is very useful. And this agent seems to be able to provide that same benefit very easily and in real time. So I think this is an important advancement.

DR. HACKNEY: I'm David Hackney. I voted yes. I think it clearly is useful to the neurosurgeon to have this information. It may well reduce the need for intraoperative MRI, which, as you heard, is both time consuming, expensive, and not widely available. And it has the potential to make the surgeons more confident and perhaps even faster in doing the operation if they have less equivocation about when they've achieved their desired level of resection. So I think it's a useful advance.

DR. JACOBS: Paula Jacobs. I voted yes. I think the data presented for both efficacy and

safety are adequate for approval of a drug in this very horrible disease and that surgeons need every tool that we can offer them to help them with their art.

DR. ROYAL: Henry Royal. I voted yes for all the reasons that people have already stated.

DR. TOLEDANO: Alicia Toledano. I voted yes. There's an extensive safety database, and in the context of this disease and in the surgeons really wanting this ability to use this product, I think it's enough.

DR. HERSCOVITCH: Peter Herscovitch. I voted yes. There is definitely a favorable benefit-to-risk ratio. And though the benefit is only going to be incremental in this extremely difficult disease, I think an incremental benefit is something that we should be appreciative of.

DR. GILBERT: Mark Gilbert, and I voted yes for all the reasons stated by my colleagues, as well as the recognition that the more patients that have a more extensive resection, the better we'll be able to look at new agents. Also with the

knowledge, like with any other technology, as our colleague use this more and more, they'll get even more facile, and the outcomes will be even better.

DR. ROYAL: Before we adjourn, are there any last comments from the FDA?

DR. MARZELLA: None other than that we want to thank the committee for a great discussion. We appreciate the feedback.

DR. ROYAL: Dr. Roberts?

DR. ROBERTS: Yes. I just wanted to implore the company to please take into consideration moving forward pediatric patients, and how useful this could be in that population as well, and to consider including them in any future trials.

DR. ROYAL: Panel members, please take all your personal belongings.

DR. MARZELLA: May I follow up on that question? Regarding use in pediatric patients, to what extent do you think that the data in adults could be extrapolatable to children? Is there enough known about the disease? Would you expect there to be -- to what extent would you want to see

trials done, randomized trials done in that population?

DR. ROBERTS: I think your question is trying to get at, if this is approved in adults, does that give us license to go ahead and start using it off label in pediatric patients.

DR. MARZELLA: No, no. That's not the question. The question is, would there be enough similarity between the disease in children and in adults to not require extensive data, but a more limited dataset to show that the product works just as well in children?

DR. ROBERTS: I think the issues concerning safety would have to be addressed in children.

DR. MARZELLA: Yes

DR. ROBERTS: I would expect that the agent would work similarly in pediatric patients as well. There might be differences as far as the infiltrative natures of the tumor and a more widespread disease, but that's the kind of questions that would have to be answered.

DR. GILBERT: So can I add to that? In the

pediatric central nervous system, cancer is much more so than an adult. Extent of resection is absolutely critical. And it's germane in the most common pediatric tumor, which is medulloblastoma, where a complete resection has a much different outcome than if there's residual disease and an ependymoma, so two of the common tumors without a doubt.

In fact, with medullo, it's so important, and ependymoma, it's so important, surgeons go back in for a second operation just to achieve that extensive resection. And if they could do it one time because they can visualize the cancer, it would be a game changer.

DR. MARZELLA: Could we ask the company if they know of any data regarding this?

DR. ROYAL: I would like to finish the committee's business. We've addressed the issue we were supposed to address. Any of these other questions that you have about pediatric applications, you can discuss after the committee meeting.

DR. MARZELLA: Great. Thank you.

Adjournment

DR. ROYAL: Panel members, please take all your personal belongings with you as the room will be cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out, so that they may be recycled. We will now adjourn the meeting. Thank you.

(Whereupon, at 2:46 p.m., the meeting was adjourned.)