FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE

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The Ballrooms
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Two Montgomery Village Avenue
Gaithersburg, Maryland

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C O N T E N T S

P R O C E E D I N G S (8:02 a.m.)

DR. RAMSEY: Good morning. Let's go ahead and begin our second day here. Again, I want to start by thanking Leander Madoo for putting together really a terrific program, from getting some wonderful experts in here to bringing us up to speed on everything, and thank all of the other people who have worked hard on this program.

So the first thing on our agenda carried over from the first day, but we've completed the agenda items from Day 1. So we'll move right into the Day 2 presentations, which begin with "FDA Presentation on the Safety and Effectiveness of Water O-15 Injection in Neurology," and the first presentation will be by Dr. Sancho, I believe, which will be "Clinical Pharmacology/Pharmacology/Toxicology."

Dr. Sancho? I think this is not Dr. Sancho.

DR. SADRIEH: No. I'm Nakissa Sadrieh, yes.

DR. RAMSEY: Thank you.

DR. SADRIEH: My name is Nakissa Sadrieh. I'm the pharmacology and toxicology reviewer for the O-15 water application, and Dr. Alfredo Sancho, sitting next to me, he will follow this presentation, and he will be talking about the clinical pharmacokinetics section of the O-15 review.

Like the other presentations yesterday on N-13

ammonia and F-18 FDG, the data that's going to be presented is going to be from this literature review.

Next slide, please.

Here's a brief outline of what I'm going to talk about. It's a short presentation. I will first cover some of the physical and biological characteristics of O-15 water, and then I'll talk a little bit about some of the known data that's available on the dosimetry, and I will end my part of the presentation with a preclinical example that was published in the literature where O-15 water was used in conjunction with PET.

Can I have the next slide, please? Thank you.

Looking at some of the characteristics of O-15 water, O-15 is a very short-lived radionuclide. Its decay half-life is a 122.5 seconds which translates into 2.1 minutes. While decaying, it emits positrons with an energy of 1.74 mega-electron volts.

O-15 water is produced in a cyclotron, and after being produced, it's diluted in .9 percent NaCl. Therefore, prior to injection, water is an isotonic saline solution, and for clarity purposes, I would also like to state that the presentations on O-15 water are limited only to O-15 water administered by the intravenous route of administration.

Water is a naturally-occurring body constituent

and is biologically inert. It has profound physiological effects. However, under the conditions in which it's going to be used with PET imaging, it's not expected to have any deleterious side effects.

The kinetics of water, of O-15 water are not affected by metabolism. This is in opposition to the other two agents that were discussed yesterday, namely N-13 ammonia and F-18 FDG. So water is not trapped in tissues. In fact, water is cleared from tissues, and the rate of clearance is a function of the blood flow to that tissue.

Water is a diffusible radioactive drug, therefore, and it crosses the blood/brain barrier. Within a tissue, it has a high extraction, and in fact, it's been reported that in primates, the extraction fraction is over 95 percent within physiological slow range.

If I could have the next slide, please, looking at some of the dosimetry data that's available, the accumulated administered dose of O-15 is absorbed internally. The dosimetry that's available is based on a study in newborn infants and in ICRP extrapolation to adults, and the critical organs of exposure were found to be the lungs, the spleen and the gonads.

I would also like to remind you at this point that the half-life of O-15 water is 2.1 minutes. Therefore, under the conditions in which it's going to be

used with PET imaging, it's not expected that significant radiation exposure would occur.

The absorbed dose is 32 to 46 millirems per millicuries. Effective whole-body dose is 80 to a 100 millirems per millicuries, and the average individual study dose range is 10 to 15 millicuries.

Could I have the next slide? Thank you.

Regarding the need for pharmacology and toxicology studies, toxicology studies could be waived for three reasons. The characteristics of water, talking about water here. It doesn't have a ligand, and radiation exposure is expected to be rather low based on what I said earlier.

There is, however, one caveat, and the caveat is that the literature information does not provide data on manufacturing procedures which might introduce some residual impurities into the final formulation, and this is going to be an application-specific issue.

The pharmacology and toxicology section of my review was based on a preclinical study which I will discuss next, which is this slide, and some additional physiological considerations were addressed in Dr. Sancho's review which he will be discussing in the following presentation.

So looking at the supported study that's

available, I would like to talk about a study that was published by Bergmann, et al., in 1989 in the Journal of the American College of Cardiology.

Myocardial blood flow was calculated using one compartment modification of the one compartment of the Kety model, and O-15 water was injected, and PET imaging was done, and the values for blood flow measurement was compared with measurements obtained with radiolabeled 15 micrometer microspheres, and this was done in 18 mongrel dogs, and the dogs were control dogs at rest, dogs with coronary artery occlusion or stenosis of about 50 to 70 percent of the left descending coronary artery at rest or after dipyridamole administration, and in dogs with global low flow to propranolol administration and hemorrhage.

Can I have the next slide, please?

The results, the salient results of this study are shown on this graph here. I hope you can see it is the myocardial blood flow determined with the microsphere technique in mls per gram per minute, and of the ordinance of the myocardial blood flow determined with PET, again in mls per gram per minute, and the correlation co-efficient was found to be .9, which is a relatively good correlation.

So at least in the myocardial system, it looks like O-15 water is a good marker for measuring blood flow. A similar study was not available for looking at cerebral

blood flow.

At this point, I will end my section of the presentation. So I went over some of the characteristics of water and the dosimetry, and I talked about a preclinical study which showed that O-15 water injection is a good marker for at least measuring myocardial blood flow.

Dr. Sancho will pick up the discussion at this point and will cover some additional physiological considerations on the mechanism of action of water.

Thank you.

DR. KONSTAM: Could I just ask a basic question? Hi.

DR. SADRIEH: Sure.

DR. KONSTAM: At the risk of being ignorant, we're talking about 95-percent extraction. I'm confused about this. Water is extracted 95 percent during the first pass?

DR. SADRIEH: Into tissues.

DR. KONSTAM: Into tissues?

DR. SADRIEH: Yes.

DR. KONSTAM: Why is that?

DR. SADRIEH: In the physiological range, it's expected that very low flow and very high flow were not going to be, you know, extracting a 100 percent. You know, over 95 percent means pretty close to a 100 percent.

DR. SANCHO: I'm going to cover this in a minute, if you'd bear with us for a second.

DR. KONSTAM: Okay.

DR. SANCHO: I'm going to discuss this. I'm here to present not so much regulatory perspectives but more of scientific perspectives.

The issue about 95-percent extraction, first of all, you need to keep in mind that like Dr. Sadrieh said, the only study or the basic study we're using, it was in animals, and, two, it was in heart model. The heart model's radically different than that of the brain model. The heart model, as you can see, is a high-flow/low-volume tissue versus the brain being a high-volume/low-flow tissue. That is one of the fundamental differences between the two, and just to re-emphasize, there are no supportive studies on the brain itself.

Now, I'll address your question about the extraction in a few seconds. Bear with me. Let me go through my slides, and when I get to that slide in particular, I'll go in detail.

This is the basic formula for blood flow used. There are some modifications depending on the tissue you're using. There's some fudge factors or correction factors, depending on who. This was a formula proposed by Bergmann, okay, in his publication from 1989, and this formula,

although it says it is used to calculate blood flow, when you look at it in reality and with the limitations in technology with PET and everything else, all the advantages, whichever way you want to look at it, it really does not just represent blood flow, but it represents blood flow and perfusion.

The other sets of formulas and other matters to calculate blood flow as well as perfusion or both, and these are some other references. Of particular note would be the last article from -- I can't even pronounce the person's name, but it's the one from 1995, in which they go about differently than Bergmann's article, and I'm not going to dwell on it, but it's just to keep in mind that there are different methods of calculating blood flow and perfusion or both.

Now, why am I making such a big issue about blood flow and perfusion? Well, first of all, as all of you have done imaging studies or read about it, and as well as you can see in the packet we provided to you, blood flow and perfusion are constantly being interchanged in the literature.

A lot of articles will say this is a good method, our data validates this method to measure blood flow and/or perfusion. The same author in one article will put the word "blood flow," next article will put

"perfusion."

The basic point is perfusion is highly dependent on blood flow. Everybody knows that, but how to really measure it is an issue of sensitivity as well as temporal issue. Can you obtain a measurement of your marker before it leaks into the extracellular compartment, which I'm going to address in a second?

Also on the articles we presented to you, I just want to make another point, that a lot of the articles used dual studies, dual imaging agent, not a single imaging agent. That way, they could validate one or the other. For instance, they would use water, and they would use FDG or they would use water and something else, and in that way, they would be able to discreetly define what water information was being provided.

Okay. The blue dots here --

DR. LINKS: Sorry to interrupt, but could you go back to the previous slide, and please explain to me the difference between blood flow and perfusion in the context of this morning's discussion, and why it's important?

DR. SANCHO: Okay. For that, I need the following slide, oddly enough. Okay. Blood flow. If you go by the traditional definition of it, you need an imaging agent which will not leak from the vascular compartment into the extracellular compartment, and if it does leak, if

it does leak, it has a measurable rate constant. Therefore, you can correct for that leakiness.

Now, that's the traditional definition of blood flow for a particular type of agent. The perfusion --

DR. LINKS: Wait. I have to interrupt.

DR. SANCHO: Yes.

DR. LINKS: I'm sorry. You didn't just define blood flow, you said a certain characteristic of an agent that might measure it. What I want you to start by is to define and distinguish between the two terms, blood flow and perfusion, not tell me the differences in agents needed to measure them. I'm not even understanding the distinction you're making about those two physiologic parameters that have nothing to do with an agent to measure them.

DR. SANCHO: Okay. I won't argue that point, but, okay, let me comply with your request.

Blood flow is by definition, is the amount of volume that goes through a portion of a blood vessel in a particular amount of time. That's it. Period.

Perfusion is the amount of fluid, water or drug or whatever you want to call it, whatever you're measuring, that leaks from the blood or vascular compartment into the extracellular compartment.

What happens beyond that, that's not the issue

here. So it's relatively two different issues. Traditionally, blood flow is only within the vascular compartment. Perfusion is the rate constant, if you want to call it that way, that goes from one compartment to the other.

Now, Jain Rakesh from Harvard and Victor Waller and Walter Wolfe from USC have both -- Jain has done mathematical models, as you're all aware of it. The USC group has done in vivo human and animal studies to try to differentiate these two methods, and they've used different methodologies, like DEMRI MRI, which can cut down on the temporal issue and really get a snapshot versus other imaging etiologies that has temporal limitations. But again, I'm not going to dwell on that.

Did I answer your question?

DR. LINKS: I'm not necessarily agreeing with you, but I at least understand where you're coming from.

DR. SANCHO: Correct. Hence, what I said. In the literature, there's a lot of discussion on this, and like I said, a lot of authors to avoid falling into this pit hole and going into discussions while I define this way, this manner, and I don't and disagree with you and so forth and so on, they always play it safe, not always, but a lot of authors will play it safe and say blood flow and/or perfusion, and they'll leave it in ambiguity, and

again this is an issue that clinicians as well as scientists have always had to deal with.

What's the meaning of each one of these terms, and what's the applicability from the clinician's perspective? It's another issue which I'm not going to go into. That's not my territory.

Okay. Let's see. Going back to this slide, this is a sketch, and I essentially already went over this slide. So I'll still go through it.

The blue dots represent an imaging agent, whatever you want to call it. The leakiness from the vascular compartment to the extracellular compartment, that's perfusion, and if it does leak, and you're trying to measure blood flow, that rate constant of how it leaks should be able to measure or calculate it and therefore include it within the calculations of your formula to correct for and be able to give an accurate measurement of blood flow.

Okay. Now, that is with a normal or standard or common imaging agent. The problem here is that it is water we're talking about. Water does not have, like Dr. Sadrieh just mentioned, does not have metabolic rates that control its passage from one compartment to the other.

Now, just to give you an example, there's been a lot of discussions, and if it's a 1-, a 2-, or a 3-

compartment model, how water behaves. The problem with that is that it's almost instantaneous, its leakiness into the extracellular compartment. So a lot of authors have gone from a 3-compartment to a 2-compartment, and they can somehow, addressing the temporal issues, in other words, how fast your machine can acquire an image, they can address that and say, well, it's a 2-compartment model versus a 3-compartment model.

I believe you addressed it, and you said water, while leaks so fast out, what do you mean with a 95-percent extraction? Well, that's what I meant, what Dr. Sadrieh and I mean. It leaks so fast from the vascular compartment that it's almost a 100-percent extraction --

DR. KONSTAM: At the risk of interrupting you --

DR. SANCHO: No problem.

DR. KONSTAM: Just a simple question.

DR. SANCHO: Go ahead.

DR. KONSTAM: You inject this agent into a coronary artery. During the first pass --

DR. SANCHO: Correct. First pass.

DR. KONSTAM: -- how much of it comes out?

DR. SANCHO: Essentially all -- well --

DR. KONSTAM: Comes out in the intravenous system?

DR. SANCHO: I understand your question.

DR. KONSTAM: Okay. The first pass extraction. What's the first pass extraction of this agent in the myocardium?

DR. SANCHO: Essentially -- well, not to give you a run-around, but based on the literature, okay, and usually not just O-15 water but deuterium water and all the other imaging agents, it's almost instantaneous. All of it leaks out. Okay. Very little remains within it, but the problem is, for instance, for dosimetry purposes, for safety relations, for safety purposes, it's considered to be a homogeneous instantaneous single compartment. All of it diffuses instantaneously into all tissues, and it's first pass issue.

Now, there's going to be a lot of arguments and discussions about this. A lot of people say a portion of it remains within the vascular compartment, hence why they argue they can measure blood flow versus -- yes?

DR. HERSCOVITCH: Perhaps I can help my colleague. The extraction fraction is defined in a single pass typically with a bolus or delta input into the arterial input of an organ, and it is defined as the amount of the tracer that goes into the tissue in a single pass in relation to the amount that's available, except for its equilibration, and one really refers to equilibration.

So for example, a tracer that is 100-percent extracted at the venus end, there will not be zero tracer, but if the water content in the tissue and blood is the same, so the tracer's equally soluble, the concentration in the tissue will be the same as in the tracer at the end of a single capillary pass, and that is defined as 100-percent extraction. It's physiologically impossible for all the tracer to be sucked up by the tissue and to have zero coming out the end.

Now, also, extraction really should be seen as a parameter, not a universal constant, and it varies, not only by tissue but physiologically within a tissue, and the brain is the best one. One can imagine that if you have a higher rate of flow of blood in a vessel, there is less time for the tracer to equilibrate across the blood/brain barrier. So the extraction is less, and in fact, it's been shown with higher blood flow with no capillary recruitment. The extraction goes down.

On the other hand, if you increase blood flow in an organ by recruiting blood vessels, so that the linear blood flow in each capillary doesn't increase, then the extraction will not fall down in spite of the increase in blood flow.

The unidirectional extraction fraction of water is less than one in brain and decreases as a function of

blood flow, especially if there's no capillary recruitment.

Does that perhaps clarify things?

DR. SANCHO: I think I misunderstood his question. He wanted a definition of it, yes. It is a ratio between the two concentrations, but hence why I mentioned or made the emphasis with my presentation that there is the two models, the 1 percent of Dr. Sadrieh in the article and the one where it's proposed here different. One is a high-flow/low-volume, and the other one is a low-flow/high-volume.

DR. KONSTAM: Well, just to nail this down. So at the end of a first pass, the concentration of this agent is going to be identical in the myocardium and in the venus system?

DR. HERSCOVITCH: Not quite. It depends on the volume of -- it's close.

DR. KONSTAM: Close.

DR. HERSCOVITCH: But not quite.

DR. KONSTAM: All right.

DR. HERSCOVITCH: It depends on the volume of distribution or the solubility of the tracer in the tissues, and water is soluble in water.

DR. KONSTAM: As opposed to microspheres, for example --

DR. HERSCOVITCH: Correct.

DR. KONSTAM: -- which have a 100-percent extraction?

DR. HERSCOVITCH: Ideally, right, if they're the right size.

DR. KONSTAM: And have zero coming out into the venous system?

DR. HERSCOVITCH: That is correct.

DR. KONSTAM: Zero concentration.

DR. HERSCOVITCH: That's correct.

DR. KONSTAM: But that's because of the exit function is zero.

DR. HERSCOVITCH: They're physically trapped. They can't get out of the capillary.

DR. KONSTAM: Right, right. But both of those could be considered having nearly a 100-percent extraction?

DR. HERSCOVITCH: Right.

DR. SANCHO: Microspheres, a 100-percent extraction?

DR. HERSCOVITCH: Yes. Microspheres, if they're built right, have a 100-percent extraction. O-15 water, using the definition that I gave you --

DR. KONSTAM: Not into the tissue, but into --

DR. SANCHO: Oh, okay. That's what I was going to say.

DR. HERSCOVITCH: Yes. It depends if you're

defining -- yes. O-15 water, if you use the definition that I gave you, how much equilibrates versus the amount that is available for equilibration, it in very low flows does have a 100-percent extraction, but as flows increase, you don't have equilibration across the blood/brain barrier of concentration at the end of a capillary transit. So the extraction goes down.

DR. SANCHO: Okay. In essence, in addition to the extraction fraction issue or the leakiness, if you want to call it that way, you need to keep in mind that there are no metabolic rate constants that control the distribution of water, which goes directly back to your question, and also to complicate matters even further, under pathological conditions, even though under normal conditions, we have these numbers and values between the hydrostatic and colloidal pressures between the compartments.

Under pathological conditions, there are no measurable or they're not quantifiable per se because it varies like the gentleman just said drastically from tissue to tissue, from conditions of the tissue itself under pathological conditions. For instance, give you a tumor scenario. You have edema. That's going to change it. How does it change it? We don't know. Or you may have an occlusion of a minor vessel. How does that affect the

tissue? We don't know. There is again no articles on this matter.

And the final slide is essentially, to conclude it, is that there are certain limitations with the literature we were able to obtain and present to you. The first one is that there are very few well-controlled studies, and, two, the dosimetry in adults is mainly an extrapolation from the article that we used that was done in children with dosimetry.

There are some spotty dosimetry information on adults, actual dosimetry, but there is no solid single study on that, and from the PK and toxicology perspective, there are no articles that tell us obviously that there are safety concerns with this product, but again, like I believe you discussed yesterday, just because there is none doesn't mean there isn't.

So but that's essentially the conclusion of this. Any questions?

DR. HERSCOVITCH: Yes. I'm sorry. I think there are a few clarifications that perhaps should be presented on the basis of your talk and that's just speaking to the major ones.

That tracer kinetic formula that you said was proposed by Bergmann --

DR. SANCHO: Bergmann, right.

DR. HERSCOVITCH: -- in 1989 was in fact proposed by Dr. Seymour Kety who is the founder of the field of cerebral blood flow --

DR. SANCHO: Correct.

DR. HERSCOVITCH: -- metabolism and pharmacologic reviews in 1989 and was used to measure cerebral blood flow in the early 1980s and in fact was only adopted by Bergmann based on the use of that tracer kinetic model in the brain.

I guess the second point that somebody made, that there's no basic studies in animals on the brain itself, in fact, in --

DR. SANCHO: No. I meant clinical studies.

DR. HERSCOVITCH: Well, but I think the previous speaker very well presented an animal validation study in myocardium published by the Bergmann group, but in fact there is a similar study in non-human primates, baboons, validating that tracer kinetic model as applied with O-15 water in baboons that was published in 1984, showing that the tracer measures blood flow, and it was compared against a gold standard intracarotid injection of tracer in the central volume principle.

DR. SADRIEH: We didn't have a copy of that paper in the list of papers that we reviewed. We didn't find anything, but I would like to see a copy of the paper

that you mentioned.

DR. HERSCOVITCH: I would almost bet lunch that it is in the Bergmann 1989 paper because the Bergmann did it in the same lab as the 1984 paper. So I would think you already have that reference.

Thirdly, the statement that the dosimetry is extrapolated from children, there was a very good paper which I was a co-author on, as you refer, in which dosimetry calculations were done in newborn infants, but there are dosimetry papers in the literature for adults which are not extrapolations of the neonatal stuff, including the Journal of Nuclear Medicine and the European Journal of Nuclear Medicine and also a paper, I believe, which Dr. Ponto is a co-author, all of which relate to dosimetry calculations in adults.

So there is considerably more data to support the safe use at least in radiation dosimetry purposes in adults that you referred to, and I think I'll stick with those major points.

DR. SANCHO: I concur with you when you say that that was the formula proposed by Kety, but Bergmann made some modifications on it, and if we go back, he incorporated a couple of fudge factors in there that Kety did not incorporate, but I agree with you, the basics. It is basically Kety's formula. I agree. I apologize for

that perspective, but the one I presented is slightly a modification.

DR. HERSCOVITCH: I would say, though, that the fudge factors may relate to the fact that Bergmann was using it for the heart, and we're talking about cerebral blood flow.

DR. SANCHO: Correct.

DR. HERSCOVITCH: So it's probably better to stick with basic studies that relate to the brain of which there are several.

DR. RAMSEY: Thank you. We'll move ahead with the next presentation, and then we will have time for questions again. Why don't we go ahead with the next two presentations? The next is "Safety and Effectiveness in Neurology," and this is presented by Dr. Patricia Love.

DR. LOVE: Thank you very much and good morning.

You've just heard the results of the pharm/tox and clinical perspectives that were based upon the literature titles that were submitted, and now we're going to move into the safety and efficacy assessment, and as we do that, I would also like to acknowledge two other members of the team.

Dr. Maboob Sobhan, the statistician, who's also the team leader in the division, and Dr. Kyong Cho, who is

the project manager.

This overall presentation will follow a format that is very similar to the safety and efficacy reviews presented yesterday, and as mentioned, also it will focus on O-15 water by injection.

Again, the guidances for establishing or providing clinical evidence of effectiveness in human drugs and biologics products as well as the guidance on medical imaging and drugs, the draft guidance formed a number of the principle foundations for the overall assessment.

This is just a reminder of some of the topics that were discussed yesterday, and particularly for this review, we will be looking at the consistency of the information and whether or not it was based on the primary analysis that was proposed in the articles, and also whether or not there was a prospective plan identified in the literature itself.

Also, in addition to the blinding and the standard of truth issues, in this database, we were able to identify several studies that had greater than 50 patients, and as far as special populations are concerned, there were a few pediatric studies, and certainly the one that had greater than 40 patients and clinical outcomes discussed also will be addressed as I go further this morning.

Indication categories. Basically the same

things that were talked about yesterday and just a couple of things to point out. For the functional indication, as you've just heard, part of the issue is that this water PET imaging is a reflection of a physiologic assessment of water. There are identified formulas that were mentioned just a moment ago.

Cerebral blood flow is an example of a functional indication that's already included in the draft guidance for evaluating or developing medical imaging drugs, and cerebral blood flow assessments per se are accepted indications for other approved radiopharmaceuticals.

Throughout this discussion, I will be using the term "cerebral perfusion" and "cerebral blood flow" interchangeably, and I'll base it primarily upon whether or not the authors of the article used one term or the other, but for purposes of our overall indication, we're considering those to be interchangeable at this point.

Disease or pathology detection is another possible indication for this product, but most of the articles did not actually look at disease specificity per se. Some did look at this physiologic parameter as a reflection of pathology, and I'll be interested in hearing your comments on where you think the overall indication should be.

As far as diagnostic or therapeutic management, again there were some articles in the clinical set that looked at how you could use the information from the perfusion assessments to actually either predict outcome of patients or determine treatment regimen. So for those articles, I was specifically looking to see whether there was an explicit statement in the article about the expected value of the information and whether the study actually tested that hypothesis, also certainly looked to see whether or not the sample size was sufficiently large to allow extrapolation to a larger population.

The literature references identified for this review came from either a list of references in the USP or from titles that were identified by the ICP, and that produced articles for the clinical base that ranged from 1983 to 1999.

Overall, as you can see from this slide, 82 articles were identified, seven of which did not use water by injection but by another method, and we did not have sufficient information in the available data to assess any prodrug transformations and the amount of radiation dosimetry or other issues. So that's why we're focusing on water.

There were seven non-clinical studies that were in the original data set. Those have been reviewed by the

previous speakers. There were three duplicates or abstracts, one on a clinical study also in cardiac patients. There were 23 individual case reports or summary articles, 36 that ranged from 10 to 39 patients, and then there were two articles on pediatrics, one in 15, one in 49 patients, and then three articles that had larger than 15 patients identified.

The ICP data also could be grouped in several disease categories, stroke, aneurysm, AVM and epilepsy, angiomas, and then the sickle cell, epilepsy or presurgical localization studies.

The first group was considered in an assessment of an ischemic model or as an example of ischemic models and using O-15 water as a reflection of that, and the others were used as mapping to look for functional areas of the brain, either normal- or abnormally-functioning areas.

As was mentioned by the previous speakers, many of the articles also used O-15 water and in combination with other PET imaging drugs or in combination with other imaging modalities. So our comments are really intended to focus on O-15 water itself and are not intended to confer any assessment of the other products or drugs that were also used.

Also, in many of the clinical articles, the actual measurement or the result of the O-15 water itself

was not necessarily reported, but instead the use of O-15 water to develop a ratio that may have been a reflection of an oxygen-extraction fraction or something else which was actually reported in the data.

So I've taken the approach in the review of looking at these articles to see whether or not by using O-15 water, one can then get to a clinically-meaningful or relevant outcome as reflected by the studies themselves.

The preliminary assessment then that is derived from these data is that there are literature to indicate that O-15 water can be used to measure cerebral perfusion in patients with cerebral vascular abnormalities associated with ischemia, hemodynamic abnormalities, occlusion and other vascular disorders, and specifically for individual study doses, this was evident in a dose of 10 to 15 millicuries on average, but there were repeat doses. There were bolus and equilibrium methods, and the doses did go higher based upon the type of study.

The two key articles that lead to this conclusion are a Grubb article published in JAMA of 1998 that was considered part of the ischemic database, and a Powers article published in Blood in 1999 that is ischemic from the standpoint of these are of patients that had cerebral complications from sickle cell anemia, and also this was taken as one of the mapping studies, and it is a

pediatric study.

I'll first look at the ischemic model, and then we'll come to the mapping model. Overall, there were 55 articles that reflected some aspect of ischemia. Some were methodology articles that we'll not discuss today. Others looked at more clinical outcomes, and as mentioned, the Grubb article was the key one, and there are also four supportive articles that I'll briefly discuss.

The Grubb article was accepted as key because, as we'll see, it was prospectively designed. It was multi-center study, had blinded image interpretation, a large sample size of 87 patients, large for these purposes of our collective assessment. There was a clear protocol with amendments identified, and there was an analysis of the patients who entered using the per protocol entry criteria as well as the identified amendments. All patients were accounted for. There was a clear end point, and there was a statistical plan identified.

Specifically, this paper reported the results of using O-15 water to measure oxygen extraction fractions in conjunction with other PET imaging agents in patients who had transient ischemic attacks, who had an occlusion identified on carotid angiography, had a CT scan to define their infarct zone.

The control patient population was also used of

normals. Those subjects had an MRI of the brain and an ultrasound of the carotid. The patients were required to meet their entry criteria within a 120 days. There was a six-month clinical follow-up of patients.

The protocol modification was that patients were allowed to have the occlusion of the carotid identified by MR angiography or by ultrasound, and also this 120-day original entry criteria was also eliminated.

There was a blinded assessment of the hemodynamics of the middle cerebral artery, and this was grouped into three stages. Stage 0 was the normal subject population. Stage 2 was those patients who had increased cerebral blood flow as measured by or reflected by the use of O-15 water volume as well as the oxygen extraction fraction, and Stage 1 was an intermediate stage that was reflecting autoregulation.

The primary end point was a subsequent ischemic attack in any territory with symptoms occurring greater than 24 hours. The secondary end point was an ipsilateral stroke and death.

419 patients were screened. 99 patients completed the study or subjects completed with 81 patients and 18 controls. There were 58 men, 23 women, 65 years was the mean age, and here the same numbers for the control.

Overall, for the per protocol requirement,

original requirement of alternated contrast angiography, 93 percent of the patients met that entry criteria, and 74 percent of the patients met the per protocol a 120-day enrollment requirement, and you see the numbers for the other groups on the slide.

The results were grouped according to those patients that had either normal or moderate abnormalities on hemodynamics, and those that had the severe abnormalities, and as you can see, the groups were similarly proportioned with 52 percent and 48 percent entering.

Of those with normal or moderate hemodynamic abnormalities, only 7 percent progressed to the primary end point of stroke, and for those with severe abnormalities, 31 percent progressed to that primary end point.

For the per protocol-entered group, this was statistically significant at P .008 for all stroke occurrences, and for ipsilateral occurrences, significant at .02, and also you see the age-adjusted independent risk shown at the bottom, and the slide also shows the results for the patients who entered after the protocol was modified.

Therefore, the preliminary assessment then is that this is a key study because of the prospective blinding aspects, the fact that the amendments were

identified. You contract the amendments and the statistical results, and based upon the overall data in the article, it appears that the method was adequate to quantitate the relative risk.

Actually, I neglected to mention about 20 other factors that were identified and analyzed in this article for potential impact on the relative risk, and only those that were mentioned were felt to be relevant.

The weakness of the article is on whether or not this relative risk can be extrapolated to a larger population. There were only 18 patients in the normal control population. So even though there was the statistically significant result, the strength of moving that to the larger population is limited, and if one was going to give an indication, such as a management indication, then you'd have to perhaps weigh the relative merits of doing that with a smaller group.

There is an error on this slide. There was a gender analysis included in the independent risk, but ethnic or racial factors were not considered, and they may affect the occurrence of stroke in some other articles.

The four supportive studies are listed here and will just be discussed briefly. The Derdeyn article is from the same investigator group as the Grubb article and was published in Stroke in 1998. It followed the same

protocol and thus had essentially the same strengths and weaknesses as the Grubb article.

The research question was slightly different and did not necessarily go as far in terms of what one can do in terms of future prediction, and because this study is from the same investigator group, generally when we look at this in an NDA review, we would consider this to be a lack of independence between the two studies, and one could either choose to lump the two studies together into one large study, if you can pool the data, or you could look at these as a key study and another supportive study, and that's the approach I chose for this particular review.

A Kuwabara study was done in Moyamoya disease, which is a rarer disorder, and it was published in Stroke in 1997. It was evaluated because it was a rare disease and a homogeneous population of 13 adults and seven pediatric patients.

Normally, adults most often have stroke symptoms, but this author selected patients that had TIA symptoms which are what's most often seen in pediatric patients and then studied again the same oxygenic extraction fraction measures that had been discussed in the Grubb and the Derdeyn articles, and so the strength of this study was that it's a prospective study with a homogeneous uncommon disorder.

The weaknesses were that based upon the information, it was not clear whether there were blinded results. Was there a selection bias because these 20 patients were derived from a larger study that was published earlier? So exactly the specifics of how these patients were selected was not entirely clear.

Also, the study gave observational reports and didn't necessarily present a statistical hypothesis that was tested. So we looked at this study as an example of another way oxygen extraction fraction can be used, but again, it was not moving us farther along in terms of being able to move to predictive statements that could be conferred.

The Powers article in Annals of Neurology in 1998 actually was an earlier study that also looked at approaches that were similar to those identified in the Grubb article, and it was a prospectively-designed retrospective analysis of 47 subjects, 30 stroke patients and 17 abnormal controls that were used to identify the regions of interest that we evaluated in this study.

These patients had similar entry criteria and a one-year follow-up on medical records. It appeared that they might have had repeat PET imaging. The article was a little convoluted about that, and it wasn't clear about whether there was blinding done. However, there was a

stated null hypothesis in this study, that if the patients had a hemodynamic abnormality, then their one-year stroke rate would be greater than a rate that was published in another article on an extracarotid/intracarotid bypass study.

That study then formed the basis of the historic control of 417 patients against which the Powers-identified studies were compared. The Powers article said that they were not able to reject their null hypothesis. So there wasn't a difference in the stroke rate, and here are the differences and the P value.

This study was reviewed particularly because it was laying a foundation for the Grubb article that was selected as key, and it did have a prospective statistical plan. The weaknesses are, however, that it was a retrospective analysis. There wasn't a lot of information to determine whether there could have been a selection bias, and the information on the EC/IC historic control were not fully discussed in that particular article, but certainly you could look at the other article for other information.

The Marchal study also looked at oxygen extraction fraction. It was published in Lancet in 1993. In this study, these patients with a middle cerebral reocclusion had symptoms for less than 18 hours, and it

correlated image patterns and course. It developed three categories which were somewhat similar to the categories used in the Grubb article but with some slight differences in terms of their definition but overall approaching the same group, and again as stated, it measured those patterns with the clinical course in these patients.

Pattern 1 was the most severe group, and they had the most severe course, and Pattern 3 approached normal, and those patients had a good recovery, and there was a statistically significant difference across these groups.

The strength of the article is that it was prospective, and they were able to find this statistically significant difference. However, the statistical plan, a prior plan, used in this article was not fully identified. So whether or not this was a chance finding, was this a post-hoc assessment was not completely clear. The sample size is small, and one could not determine fully whether or not there was any image selection bias.

So for the ischemic model then, we have one key study, and for other studies that are certainly considered supportive for various reasons, they are looking at the same oxygen extraction parameter. The results seem to be consistent, and there is a trend over a period of years of moving from earlier studies in a retrospective approach to

prospective studies that are looking at the same thing and having trends that are going in the same direction.

Moving to the mapping model, there were 15 articles that were identified in the provided literature. One was an ischemic model, one in seizures, and then 13 that looked at localization of normal areas of the brain.

In this group of 13, there were three duplicate or summary articles. One was an abstract of 10 patients. Three articles reported on the results of 10 to 15 patients, and six articles reported on the results of less than eight patients.

The key article, as mentioned earlier, is the Powers article published this year, and then there were three other supportive articles.

The Powers article looked at cerebral vasculopathy and sickle cell anemia patients and the diagnostic contributions of positron emission tomography. This was published in Blood in 1999, and as also mentioned earlier, it has three important aspects. It's an ischemic model, a mapping model, and a pediatric study.

Specifically, it was prospective, looked at 49 patients with stroke and considered the added benefit of O-15 water, FDG, F-18 FDG and MRI on the detection of cerebral vasculopathy.

The article did not clearly identify a standard

of truth per se in those words, but in looking at the article and making some review interpretations, it's possible to consider the MRI and other study results that looked at intelligence testing as a reflection of cognitive abnormalities as potential standards of truth.

O-15 water was given at a maximum dose of 70 millicuries. It's not entirely clear, but it seems that there was a likelihood that this was either an equilibrium method or there were repeated small doses of O-15 water given. The statistical evaluation was chi square with a Bonferoni adjustment for multiple comparisons.

Again, patients were lumped into three groups. This seems to be a trend for all of the different articles. The grouping here reflects the neurologic defect. Category 1 is those patients with stroke and overt CVA symptoms. Category 2, soft signs or a history of a preceding illness, that was hypoxic, and Category 3 was those patients who at the time were normal and did not have a hypoxic event. Again, 49 patients, and the age of onset of the neurologic defect was at age of 1.8 years to 16 years of age.

This slide is a composite of information contained in the article. It's derived from two tables as well as the text in the article, and it compares the clinical categories with abnormal intelligence, result testing, the PET image and the MRI results.

The first column is the categories, Category 1-CVA, soft signs, and then normal patients. The intelligence quotient, which is the full-scale intelligence quotient, and then the far two columns look at the composite of all abnormal PET images, all abnormal MRI images, and then the middle three looks at the individual results of the PET images with FDG alone, O-15 water alone, and then both O-15 water and FDG.

A couple of things to note. The overall enrolled patients are 49, and all 49 patients had images regardless of the type, but only 40 patients actually had the intelligence testing, and that's either because the patients did not receive consent from the parents or because the patients were not cooperative enough to have an intelligence test.

What that means then is that a direct/direct comparison of the results of patients who actually had the intelligence with the PET images are not possible. You can't do a 1:1 analysis, but we can look at trends. So in the review, my perspective was to look at the percentage of patients in each of these groups in comparison to their overall categories and to look for a trend analysis.

So for a Category 1, the patients who had a CVA, 93 percent of patients had an abnormal intelligence test, 89 percent had an abnormal PET image, and 79 percent

had an abnormal MRI. So roughly speaking, it appears that the PET percentage is closer to the percentage of patients that had an abnormal intelligence test, and most of that is conferred by the combined use of O-15 water and FDG.

For the soft signs, 94 percent had an abnormal image, 65 percent abnormal PET, 30 percent abnormal MRI, and again most of it from the combined use of PET. The author suggested maybe the PET images are more apt to be predictive of what's happening or the development of a cognitive abnormality.

In the normal category, only 44 percent had an abnormal IQ test, 60 percent had an abnormal PET, 10 percent had an abnormal MRI, and for that reason again, the author suggests that these are the type of patients that might benefit from a more aggressive treatment, and they did provide examples in the article of patients who had transfusion treatment for the sickle cell anemia and suggest that on repeat testing, these patients showed improvement in their IQ tests.

The article, however, was not able to go further to test this and actually suggested that more work is going to be needed and further study to see whether or not this is going to be a suggestion for treatment benefit that should be followed in the long run.

So this study is accepted as a very strong

study because it's prospective. It's blinded. The statistics are described. You can do comparisons. We can at least assume a standard of truth, and it is in a pediatric population that's difficult to study.

The weaknesses are that the standard of truth is not explicitly stated, and you don't have the 1:1 correlation with the IQ test. It strongly suggests perhaps something that can be considered for future treatment, but it is not confirmed in this particular study.

Just briefly then, the other three articles in this category that were considered supportive, one was the Breier article in Neurology, 1997. It looked at 50 subjects, 34 complex partial seizure patients and 16 controls. These subjects had EEGs, MRI, SPECT and neural psychiatric testing, the same type of testing that was used in the preceding article, and in this study, both O-15 water and FDG were used.

The clinical end points were not fully defined in any statistics relevant to that, but an asymmetry index was defined. The observational results were reported, and these results were compared to the time of seizure onset, duration of seizures.

There was a statistically significant correlation between the duration of seizures and that asymmetry index. The correlation was slightly better with

FDG than with water. The IQ results were not presented. This is just a slide taken from the article that shows the correlation, the statistically significant correlation. This is the asymmetry index on the left, the duration of seizures on the right, and here is the control group.

So this study was a prospective study of 15 patients, involved several comparisons, and on identification of a test factor of the weaknesses, it lacked a clear clinically-relevant end point. The statistical hypothesis was not stated. The IQ results were not presented.

Moving to the eloquent cortex, this is identification of areas that are relevant to the normal brain and perhaps have been used or are being used to guide surgical assessments.

There was a Vinas article of 18 patients without controls. This was published in Neurologic Research in 1997. It evaluated the results of presurgical and intraoperative brain surgery guided by electrical brain mapping results. It looked at O-15 water, PET. There were five brain test tasks that were studied. Each of those was imaged twice, and there was a 10-minute delay between each image set.

The tasks were resting, finger to thumb motion, listening to something, listening and then repeating words

or simple sentences, and then visual stimuli with a comparison of the right and left half fields.

In this study, as I said, there were 18 patients. Here's the mean age, and the age ranged from eight to 74 years. 15 tasks were done for language, five were done for motor localization, and obviously there were some patients that had more than one task set.

The motor areas co-registered for PET and MRI in the gray areas but not the white. That meant the PET images identified the same site for the normal eloquent brain as well as the site that was identified for surgery, and in the language of tests, all areas were concordant.

The article presented two patients that had full recovery on the basis of these image results and the change in the surgical procedure. The other patients were not fully discussed.

So the strength was that it did have a clinical outcome. The weaknesses, it's a small study. It did not have an actual statistical plan. This was just an observational set, and also there wasn't enough information to determine how these patients were selected. Was there an image bias? Were the images blinded or not? And what was the expectation of the outcome had the different surgical plan occurred was not fully discussed.

The Duncan article is the other pediatric study

that was published in Pediatric Neurosurgery in 1997. It appeared to be a prospectively-designed retrospective series of 16 pediatric patients that were going for surgery.

It had a hypothesis that PET optimizes the presurgical evaluation in these patients, but a statistical plan or whether or not blinding was done to evaluate this hypothesis was not stated in the article. O-15 water was given in doses from 25 to 50 millicuries, and the results were again co-registered with MRI, and the task imaging studies that were done were similar to those of the previous article.

In this population of 16 patients, 15 had co-registration of the PET images with MRI, again identifying the same site for the eloquent cortex as well as the site that was identified for surgery.

There was a greater listing of the patients in this particular article than in the preceding article, and in 12 of the 15 patients that had co-registration, the surgical plan was changed, and in three of those patients, surgery was changed to a medical management or other treatment modality.

The strength then is this is another pediatric population, and there are clinical outcomes. The weaknesses, you cannot eliminate an image bias or a

selection bias. A statistical plan was not identified. Also, for both of these studies, the studies themselves did not contain a knot of information on the relevance of the testing itself, and that's probably in a different database, other than the PET imaging database that was provided that may be in the neuropsychiatric or other literature, but that was just not available for our review at this time.

Therefore, the preliminary efficacy assessment is that the ischemic model demonstrates that O-15 water measurements of abnormal perfusion can occur, and that there do seem to be relevant clinical settings for that used, and the sickle cell anemia study provides some information to support the use of these measurements to identify other types of abnormally-functioning areas.

As far as the normal brain function is concerned, as mentioned, the articles are small. Actually it's less than 18 patients. Most of these are research studies that are looking at the development of new techniques or treatment modalities, and some of the information that was just mentioned was not available at this time.

However, on the other hand, this is somewhat intuitively appealing. You're doing studies. You're actually seeing a result right then. You're in the OR, and

this is information that's able to help perhaps pinpoint some areas of or further pinpoint areas of what we already know about the existence of neuroanatomy.

So I'll be interested in hearing the community's comments on this aspect and whether the extrapolation of the abnormal data can be justified at this time to normal areas of the brain.

As far as safety, most of this was discussed by Dr. Sadrieh. We don't have any information in the articles on whether there was actual monitoring of adverse events during any of these studies, and water actually was not identified in a recent publication on the safety of radiopharmaceuticals.

On the other hand, this is water. We know about it. We know how water behaves in the body. We know, since this water is injected in saline, we're not concerned about tonicity effects. We're not concerned about nitrogen balance effects when O-15 water decays to nitrogen, and also we know about the radiation exposures. So we're not having safety concerns from this perspective.

So then, in summary, the review preliminary conclusion is that O-15 water effectiveness can -- is in the use of O-15 water to measure cerebral perfusion in patients with cerebral vascular abnormalities associated with ischemia, hemodynamic abnormalities, occlusion and

other vascular disorders, and as I said, I'd be willing to hear other comments.

Thank you very much for your time.

DR. RAMSEY: Thank you, Dr. Love. Unless I hear an overwhelming need for questions, I'd like to go ahead with the next presenter, and then we'll have time for questions after that.

DR. KONSTAM: Just a factual question for Dr. Love.

DR. LOVE: Yes?

DR. KONSTAM: The Grubb and the Derdeyn paper, you mentioned that was from the same group.

DR. LOVE: Yes.

DR. KONSTAM: Were they different populations?

DR. LOVE: They used the same control population. It sounds like they might have been different populations. It's not entirely clear, but my assumption is that they are two different populations. Same protocol.

DR. KONSTAM: Well, I just want to point out, you know, I think it's a different order of magnitude of a problem.

DR. LOVE: Yes.

DR. KONSTAM: If it's saying, well, the same group with clearly a different study reproduced it, but once you say there's a possibility that it's in fact the

same patients, then I think that's a bigger problem.

DR. LOVE: I absolutely agree with you. I did look at that. I read the Derdeyn, however you pronounce that --

DR. KONSTAM: I don't know.

DR. LOVE: -- two or three times to try to actually answer that particular question. My assumption is that they are two separate populations, but the article is not entirely clear, and you could make the equal assumption that it is the same population, and for that reason, I did not lump the two articles and just accepted them as supportive information.

DR. KONSTAM: The other question I had, the principal sickle cell paper did not have a control group in it. I guess they just studied sickle cell kids.

DR. LOVE: They just studied sickle cell children, but one of the three groups of children was normal on their categorization of clinical symptoms. They did not have current signs, and they had not had an identified stroke. So you could look at that as a spectrum of patients.

Other questions?

(No response.)

DR. LOVE: Thank you.

DR. RAMSEY: Thank you, Dr. Love.

Dr. Conti?

DR. CONTI: Good morning. Peter Conti from USC, and I want to again thank the committee for allowing us to present this data from the public and also commend you on your activities and actions yesterday. This was a very useful discussion from our perspective and the public to hear and understand how the interactions occur. I thought the scientific questions in particular were very relevant.

What I'd like to do is again go back to my earlier approach of PET 101 and give you some of the practical clinical examples of how we would use O-15 water in patients.

If you remember yesterday, we were able to show -- maybe we can turn the lights down a bit for these slides. See, those of us in the public sector don't have the ability to have the high-tech that the FDA does in terms of the computer presentations. So we have to revert to old slides.

I mentioned some of these clinical tracers as examples, and we talked about FDG and N-13 ammonia, and then obviously we're talking about O-15 water now, and again just another reminder, this is a positron isotope. Again that's the two-minute half-life which means it's very difficult to make many sophisticated molecules with O-15

because of its short half-life, but certainly something like O-15-labeled water is relatively straightforward, and hopefully in the future, we'll be talking about other compounds, such as those dangerous substances as oxygen and things like this down the road.

Yesterday, I also mentioned in neurological and neurosurgical applications for PET, that vascular abnormalities are one of the key indications clinically. We talked about some of the applications earlier in my presentation in epilepsy, dementia and movement disorders, but we're going to focus here on vascular or cerebral abnormalities.

Now, there is a rich history of using perfusion-like agents in the nuclear medicine world. This is actually a technetium-99m HMPAO study in patients with Alzheimer's disease, where you can actually see alterations in perfusion of the brain with this drug in what was a classical pattern for Alzheimer's disease in the parietal bitemporal lobe distribution similar to the FDG scans that I showed you yesterday, but again based on a perfusion imaging tracer.

We also noted earlier this morning in this morning's presentations that O-15 water can be used to image the heart as a perfusion agent, and we could see these images of the heart and these lung axis views. These

are patients that are being treated with TPA following an anterior infarction in this particular case, and you can see the recovery of perfusion following the administration of TPA on serial images with O-15-labeled water. In this particular study, it was compared with Carbon-11 acetate.

Now, again blood flow images can now be obtained in the very simple fashion following intravenous administration of this radiotracer, and the studies that we've done, particularly at USC, a lot of them have been comparisons between flow in this case or perfusion, if you will, with glucose metabolism.

I have to say on the outset that a lot of the blood flow or blood perfusion -- I prefer the word "perfusion" as you have shown on your slides -- are based on extensive data from animals and animal models. So my discussion here will focus primarily on the clinical applications, and I do appreciate the discussion of the basic science as a foundation for these radiotracers.

As you can see, the O-15 water images do provide reasonably good high-quality images for clinical interpretation.

Now, let me just begin by showing you some examples of stroke. This is a classical middle cerebral artery infarction, seen both on the FDG scan and blood flow images here. You can see the large deficit in what is a

classical middle cerebral artery distribution following an ischemic event in this patient and actually a very matched defect, if you will, in the flow images. It actually looks a bit more extensive on the blood flow images compared to the glucose scans, and this may represent the improved ability of O-15 water to detect areas of ischemia as opposed to FDG looking at straight infarction.

Now, we've done some extensive work in sickle cell anemia, and you've seen some of this data presented already, and I just want to give you some of those examples to go along with that clinical paper.

These are children who a large fraction of which will go on to develop overt clinical stroke, and this is a relatively devastating disease for many of these kids, which is the main driving force behind our study.

Many of the children have signs, clinical signs. Many of them also have neurological imaging studies, such as MRI, that do display areas of presumed infarction, and some of these findings on MRI scans don't necessarily correlate with the actual clinical symptoms in many of these children.

So MRI has been used more or less routinely in patients with sickle cell disease, and here's an example of a T2-weighted MRI scan showing areas of increased signal on both hemispheres, suggestive of areas of stroke or

infarction. Another one here.

MRI has also been used extensively now in children with this disorder. This actually turns out to be a normal MRI, but again we would use this as part of the serial neuroimaging that would be done in these children.

This is the same patient with a PET scan. The upper images are flow, and the lower images glucose metabolism. In this case, it's a fairly reasonable concordance between the amount of glucose metabolism preserved and the flow preserved. You could see deficits here and here, and if you go back on that MRI scan, we'll just jump back for a second, you can actually see that there are in fact lesions here and here similar to what you saw on the PET studies.

I think the PET studies do provide an added dimension of the extent of that disease that's not appreciated, for example, on the MRI and the study.

Here's another example. You can see these types of lesions that occur in sickle cell disease here and here, and again more extensive disease seen on both the glucose metabolism as well as the blood flow studies, multiple infarctions and areas of ischemia.

This is a more advanced trial, actually over 18-year-old adults with some of the sequelae that can happen after you get multiple ischemic events in sickle

cell disease. You can see basically what's left of the brain in this particular case. Most of it has infarcted, and these children are severely retarded, and this is, as I said, a very devastating disease for these young children.

Now, there are examples, as I alluded to earlier, that there is some discordance between the glucose scans and the ischemia in the blood flow studies, and you can see, for example, here and here, there's an area of infarction on the metabolism study, but you can see there's a bit more extensive findings on the blood flow, suggesting that these areas are perhaps compromised vascularly, and we should be aware that this area is at risk, and this is the type of child that we'd want to make sure we got into a program to preserve what is left of that brain through more aggressive transfusion-type therapies.

Now, it's beyond sickle cell disease that we have other areas of stroke. I mentioned middle cerebral artery infarction earlier, and, of course, there are other reasons for stroke, and this is an interesting case of a child with a mixed cell leukemia who comes in with an MRI scan showing an area of enhancement and some signal changes in the white matter here, and the issue in this particular case was because the child was receiving intrathecal methotrexate for treatment of the leukemia, and methotrexate by that route is known to also cause cerebral

infarction, whether or not this actually represented a site of infarction or recurrent tumor. So it was a little bit tough just from the MRI study.

And we actually used the glucose and flow studies here to show quite clearly that there was an area, a wedge-shaped area of decreased metabolism. This was not the recurrent tumor, and it was more likely to be stroke, and you can see in fact that there's a little more extensive ischemia than there is on the glucose, that there's some preservation, if you will, of some of the surrounding cortical matter on the glucose scan, but there was clearly areas consistent with ischemia beyond that stroke.

Now, this was another complicated case. This patient had this MRI scan and a long rich history of cardiovascular disease, and it was presumed that this would represent either some sort of malignancy or perhaps a stroke which can present with enhancement and mass effect and some other parameters that you can identify on this MRI study, and here's the T2 image shown here.

Now, this lesion was biopsied, and it came back with a fair amount of necrosis, and it was consistent when all was said and done with the presence of debris related to a prior stroke, and the patient was treated conservatively, but the disease and the symptoms

progressed, and at one point, the patient came in for a PET scan.

I apologize. These images are not high-quality. The patient actually was a little difficult in terms of motion and movement, but basically what we were able to see on the flow studies was areas of increased perfusion as well as, again it's difficult to visualize, areas of increased metabolism on the FDG study as well.

These two findings are not consistent with the presence of stroke. They're more consistent with the presence of malignancy and a vascular malignancy at that. This patient went back for a rebiopsy on the basis of the PET scan and in fact turned out to be a high-grade glioblastoma that had been progressing while they were treating her for cardiovascular disease.

This is another interesting case where the flow study also helped us out. This was a patient that had a prior glioblastoma, and we don't see that in this particular image, but also had this subtle finding here, this mass effect you could see. This is an enhanced T1 MRI. You can see this low-density lesion right here. Okay? It doesn't enhance very much, and it was suspected that this perhaps could represent some sort of sequelae from prior radiation therapy, a low-grade tumor, infarction, a variety of different possibilities, but given

the fact that he had a glioblastoma originally, it could represent an additional lesion. Here's the T2 MRI. You can see this lesion is relatively homogeneous.

Now, it was considered to biopsy this lesion, and again we were asked because of the history of glioblastoma to look at this from the FDG point of view, but, of course, then a lot of these primary lesions were also doing flow studies to learn a bit more about how to handle these from a neurosurgical point of view.

Well, clearly on the FDG scan, this was hypometabolic. In that scenario, differential diagnosis is infarction. It is something like a low-grade brain tumor, okay, or some other benign entity.

Now, the flow study is interesting here because the increased blood flood eliminated the possibility that this was an infarction. We knew in fact that this was a primary brain tumor of some nature, and in fact on the basis of both the FDG scan and the flow study, this was probably a vascular low-grade tumor.

This patient went on to biopsy, a very careful biopsy because of the vascular nature of the tumor with the appropriate operating room on standby because these can bleed out rather extensively on biopsy if you're not careful, and it was successfully biopsied and turned out to be a low-grade brain tumor, highly vascular low-grade brain

tumor. So I think we actually helped in the approach and diagnosis in that particular case.

I'll show you three quick examples of aneurysms which are other vascular lesions that I think can benefit from the use of O-15-labeled water. These are the perfusion scans on your left and FDG metabolism. It's a large aneurysm. You could see the elevated flow in this and the feeding vessels and the draining vessels as well.

You could see that the lesion is very extensive, and in that area, it's essentially photopenic on the FDG scan as you would expect, but also note that in fact, there is some area of decreased metabolism peripherally to this aneurysm, and this is the area that we're worried about as far as stroke, and, of course, after these aneurysms are resected vasospasm.

Another example of aneurysm, low FDG accumulation and very high perfusion, and the third example here again with very low FDG accumulation and very extensive perfusion. Again, it helps sort out the nature of the particular lesion, particularly if you don't know what it is, in a new diagnosis.

Now, in terms of other neurological entities, this is obviously a very large lesion. Meningiomas tend to be extremely vascular tumors, and it also helps sort out meningioma from other types of malignancies in many

circumstances.

Meningiomas tend to display a significant amount of glucose metabolism, not as much as your high-grade brain tumors, but certainly more than an aneurysm. So again it's in that spectrum of the types of intracranial lesions that we'll see, but knowing this very high blood flow which is very typical of meningioma again helps sort out exactly what we're dealing with.

In this particular case, obviously this is a gross extractual lesion. So we were not very concerned about the specific diagnosis, but I can assure you there are many that are complicated.

For example, here's another one, again very low glucose uptake in this particular case, but here, there is flow in this meningioma in the base of the brain here. You can see elevated perfusion.

Now, in the differential diagnosis of benign versus malignant, we don't want to necessarily get into the argument that O-15 water can be useful in that particular arena because it is not, and in fact, this is a good example of a type of patient that has multifocal glioblastoma.

You can see one of the lesions here in the cerebellum. You can see the inferior aspect of another lesion in the temporal lobe. I don't have the other MRI

with me, but I can assure you there are two lesions, and you can see on the FDG scan clearly both lesions are hypermetabolic. Here's the tumor here. Here's the second tumor in the temporal lobe, and if you'll look on the flow studies, interestingly, this particular lesion is vascular, and this particular lesion is relatively avascular. Which would you biopsy? Well, probably this one if you wanted to assure yourself of not getting into a little bit of a flow problem at your biopsy. This is the type of practical information that would be helpful here.

Now, I just want to mention a couple of points on the activation studies. Somebody said it's nicely blocking a UCLA thing here, which is appropriate. No, I'm just kidding, George.

But in any event, this is from my colleagues at UCLA, using normal subjects and doing the stimulation responses which you may have seen in the literature as far as classical uses of brain mapping, and you can see that with the right stimulation, you can activate various areas of the brain, and, of course, depending upon where the lesion is, you may want to stimulate certain areas of the brain to see the proximity of those eloquent centers to the lesion of interest prior to surgical resection.

This is the type of thing that we can do with O-15 water, and this is one of the examples from the

literature showing the co-registration on an MRI, if you will, 3-D MRI, and these areas are various areas of mapping following the appropriate stimulation, namings, other types of challenges that the patient receives, and the pink area here, for example, represents the tumor, and you can see that there are some overlapping challenges on the area of the tumor.

This type of approach is very useful from the neurosurgeon's point of view because you can minimize the deficits associated with the surgery by preserving certain regions that are in close proximity to the tumor. Many of these patients usually go on to incomplete resections because of the extensiveness of the tumors. So to try to achieve a complete resection is not always possible.

If you're going to spare certain things, you might as well spare the areas that are going to preserve the most function for the patient, given the fact that they're likely to die of their disease, and you want to improve the quality of their life for the remaining period.

Here's another example showing in this case a remote site of activation from the lesion seen here on the MRI. Here's the site of activation that's overlaid on the MRI study, and one last example in a non-malignancy. This is an AVM showing you -- here's the angiogram of the AVM.

You can see the lesion here is a baseline, has

increased to a flow in this particular lesion, and you can see with the activation here, the stimulus is very, very close proximity to the AVM but allows you again in your surgical procedure to be very cognizant of the location of that stimulus and to try to preserve as much of the cortical activity as possible.

This concludes my presentation. I'll be glad to answer any questions regarding O-15 water studies.

Thank you.

DR. RAMSEY: Thank you, Dr. Conti.

I think we'll now open the floor to the committee discussion portion. So I'll open the floor to questions from any of the speakers this morning or any other comments. We could turn the lights back on, I think.

DR. KONSTAM: Dr. Conti, can you stay up with us? I just have a few questions. I just want to a few things about sickle cell disease.

First of all, I just want to congratulate you on your presentation. I mean, I think those were some fabulous illustrations of how this agent could be put to good use.

Just educate me a little bit about sickle cell disease. First of all, are there any studies that have looked at specifically O-15 water and findings on PET and how they relate to clinical prognosis in any way?

DR. CONTI: In sickle cell, not to my knowledge. There are only two other papers that I'm aware of that were published a few years back, one was using O-15 water with oxygen, and these were actually adult sickle cell subjects, and there was a smaller article using FDG and O-15 water, again a very small population. I think six patients or something like this back at the NIH, I believe it was done.

But there's no data that I'm aware of that really shows prognostic information. We alluded to that in our articles, Dr. Love pointed out. We felt that this is something that we'd like to study a bit further because I think it's very important.

DR. KONSTAM: Well, you know, I'm just trying for myself to get a flavor for how, you know, in this particular disease as an example, how this agent might be used by clinicians, and what impact it really will have on management and outcome, and you showed a couple of pretty devastating-looking pictures, and the question is, how does that influence therapy is the question for me.

So maybe you could educate me a little bit about the therapy for sickle cell disease and specifically how the findings that you have there would influence your therapy and why or what evidence do you have that that would make a difference?

DR. CONTI: Well, I have to admit, I am not an expert in treating sickle cell patients. So you have to bear with me, but certainly transfusion therapy is probably of the more aggressive treatments that are offered to these patients. There are some chemotherapy-type approaches that are used. Hydroxy urea is another example.

But transfusion therapy is more or less the treatment of last resort, if you will, for aggressive therapy protocols. So let me start by saying that and then just mention that the type of practical applications could be examples, such as the following.

We've studied some of these children within families. So for example, they may have three or four children. The older child may have a ready-exemplified stroke, clinical stroke. His younger brother, for example, may be having trouble in second grade, and, of course, the one-year-old, we don't have any signs or symptoms.

Within a family, it gives you some perspective of what's going to happen to those younger children if you look at the older children from a clinical point of view, and we know that there's already a trend in that family. That family, once identified, then could be studied at an earlier age before overt symptoms occur, and in fact, if they are displaying abnormalities on the PET scan that's not detected by the conventional imaging or by clinical

examination, they may be considered for more aggressive therapy given the track record of their siblings because there does tend to be some sort of familial relationship with the aggressiveness of the disease.

Likewise, a patient that has had symptoms and may go on to receive such transfusion therapy, we can repeat those studies. I think we did show an example of that type of case in the paper where we felt that on repeat studies following aggressive transfusion therapy over time, that we can use PET to more or less monitor the resolution of ischemia with the therapy.

So from a point of view of identifying at-risk subjects or in a high-risk patient population, that's one practical side of it. On the other, to specifically follow the therapy in an individual patient is a second practical side.

DR. KONSTAM: Well, I guess my last question would be do either you or are you aware of anyone who's actually conducting or planning to conduct a perspective study to either look at the impact of PET or the relationship between PET and outcome or even more importantly would be specifically how PET influences therapy and whether that actually resulted in any benefits?

DR. CONTI: I'm not aware of it myself. We would like to do the study ourselves. We're trying to

receive funding for that, but I would also tell you that people in the MR world are also approaching this as well. So there probably is some overlapping literature using other diagnostic tests as well with the same goal, to correlate with outcome.

DR. PONTO: Dr. Love, I am very confused by your selection of literature. I guess my question is if we were looking at a functional type of indication, where we're looking at this as the effectiveness of this particular agent to measure blood flow, why did you essentially ignore all of the mapping literature? Because all of that has normal controls. It has statistical methodology that has been very well proven to isolate areas of function, and also has a number of groups, such as work that I've done at my own institution with schizophrenics, with panic disorder patients, and a number of other groups.

DR. LOVE: Basically, as was stated in the presentation, the review was based upon the articles that were submitted by ICP. So we selected from what was available, and the largest studies were the ones that I presented.

There were some methodology articles in the database, but the comment that I was making earlier that there probably are other data available that can validate some of the task methods is basically reflecting what

you're talking about right now.

So all of the reviews, both this one and the others yesterday, were based upon the articles that were provided to us.

DR. PONTO: I thought, though, that you said that you did your own searches through the databases. I mean, there's literally hundreds of articles out there on brain mapping work with O-15 water.

DR. LOVE: For O-15 water, the FDA search was not done. It was just based on the information as mentioned, the USP and the ICP articles.

DR. RAMSEY: Any other questions? Comments?

DR. LINKS: Just to get some guidance from the FDA in our thinking and sort of for radiopharmaceutical approvals in the future.

I think what's happening this morning is a further example of some of the difficulties yesterday in our discussions about using what I'll call diagnostic accuracy or disease-based literature to try to support a claim of functional assessment.

Obviously all of us in nuclear medicine love functional assessment and want you guys to support claims of functional assessment.

I'm a little worried, though, that what I perceive as a reluctance on the FDA's part to accept what

I'll call pure studies that simply validate the claim that a particular radiopharmaceutical measures or assesses or evaluates a particular function, and so I'm wondering, are you willing to accept that? What would it take for you all to accept that? Can carefully-controlled animal studies form the bulk of the evidence, and to what degree do you require studies of the application of that technique in disease populations?

DR. LOVE: I think part of that goes to some issues that are still under discussion as far as the guidance document is concerned and how we're going to approach that.

I think part of this, when we do the review, we do take into account all of the different aspects as was mentioned yesterday, and obviously the mechanism of action clearly is relying on the animal data and the known formulas and such that are being used to measure cerebral perfusion. So we're looking at that.

But the other aspect of this is that these products have a clinical usefulness in some way or another in a patient population. So we have to move from what is the actual measurement to what is its relevance in the patient, and how is it going to be used?

But there are many different approaches that can be taken to do that, and that's some of the aspect of

things that were mentioned in the guidance document in terms of different approaches, different populations and the like.

In a sense, I think what your question is going to is how would we develop a product prospectively versus how are we going to move towards an indication when you have a large database that's out there, and you're retrospectively looking at that database and trying to determine what those data actually provide, and how can we actually label this product?

But I would be very interested in hearing the committee's discussion of that, and whether you think, on the basis of this data, would you recommend that we move forward to a broader indication, one that deletes some of these other terms that are in the indication or not?

We've taken the approach based upon where we are, but that's why we want to hear your comments and see if there's something else that can be done with the indication.

Thank you.

DR. KONSTAM: Can I just voice a contrary perspective on this? You know, I think I have a fair amount of support for the concept of a functional indication, and I understand the points that you and others are raising about this, but I think there has to be another

perspective that adds into this, and I mean I think listening to Dr. Love really being defensive about the requirement to have clinical studies is part of an indication and makes me extremely queasy.

You know, to look at it on the other end of the spectrum, there's a whole world out there that is saying that we need to practice medicine on the basis of evidence, clinical evidence, evidence that what we do in medicine influences outcome, and now I have to say, on a personal note, in other forums, I have challenged what I've considered some extreme expressions of that view. But this is a different forum, and I don't think that the view of a requirement for evidence-based medicine is sufficiently represented in this discussion.

I think that there needs to be, it sounds to me, a great deal more thought placed into reconciling these two perspectives, of saying when you're doing an imaging study, you know, if it tells you something about function, maybe that's enough. Maybe we need to say that's approvable.

I find that a very extreme notion, and I guess, just thinking about my own comfort level reconciling what I see as these two extremes, really, I would say that if we want to continue with the concept of a functional approval, then I would at least create and hold us to some kind of a

standard of some reasonable degree of clinical data set that gives us at least a decent comfort level, if not perhaps the same levels of standards of evidence that are asked for in other forums, but at least some reasonable comfort level that we're making an impact on clinical care by doing these functional assessments.

And, further, I would say that in approving an agent for functional assessment, I take the position that I hold the FDA to help us a little bit more than that and say in the packet insert for functional assessment, but here are the types of clinical actions or clinical goals that you might expect, and here's the evidence that supports it, and I think that that's not too onerous a standard to expect in this kind of an indication.

DR. LINKS: I understand what you're saying. My concern is that the interpretation of reasonable demonstration might make it too onerous. Here's why I'm concerned.

In the old days before the final rule and the proposed guidance, when push came to shove, every medical imaging drug submitted for us to recommend approval or not was really judged on diagnostic accuracy. No matter what else you want to say, what we ended up talking about were sensitivity and specificity, and I personally believe that these four indications, which are dramatically different