DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT DRUGS

ADVISORY COMMITTEE

Thursday, May 16, 2002

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Chair: Nathaniel P. Katz, M.D.
Executive Secretary: Kimberly Topper, M.S.

MEMBER
Janice Bitetti, M.D.

INDUSTRY GUEST
Charles H. McLesky, M.D.

CONSUMER GUEST
Thomas Foster, Pharm D.

PATIENT REPRESENTATIVE
Yvette Delph

CONSULTANTS
Solomon Aronson, M.D.
Michael Ashburn, M.D., M.P.H.
Vera Bril, M.D.
Robert H. Dworkin, Ph.D.

GUEST SPEAKERS
David Cornblath, M.D.
Eva Feldman, M.D., Ph.D.
Michael Polydefkis, M.D.
Michael Rowbothom, M.D.

GUESTS
Peter Dyck, M.D.
John Farrar, M.D.
Mark Rendell, M.D.
Steven Shafer, M.D.
David J. Wlody, M.D.
Clifford Woolf, M.D., Ph.D.

FDA STAFF
Cynthia McCormick, M.D.
Gerald Dal Pan, M.D., M.H.S.
Sharon Hertz, M.D.
Bob Rappaport, M.D.

C O N T E N T S

P R O C E E D I N G S

Opening Remarks

DR. KATZ: Good morning. This is the meeting of the Anesthetic and Life Support Drugs Advisory Committee. We will be speaking today about neuropathy, clinical trials and neuropathic pain. So, if that is the meeting you are interested in, you are in the right place. Otherwise, they can help you find the right meeting outside.

My name is Nathaniel Katz. I will be chairing the meeting this morning.

What we will do now is I will just make a few brief introductory comments and set out some ground rules for everybody. We will do introductions and then we will have a welcome and introductions from Dr. McCormick.

First of all, the topic, again, that we will be speaking about today is clinical-trial issues in patients with peripheral neuropathy or neuropathic pain. I would like first to extend my welcome to our invited guests. We have managed to assemble a great group of individuals here who really are the true thought leaders in this area so I am sure we will have a very productive discussion

today.

In terms of some concrete ground rules for the people around the table, there are a few things that you have to know that will make the meeting work. First of all, when you speak, you have to speak into the microphone because everything is being recorded, so don't forget that. I will be sort of obnoxious. When you forget the first few times, I will cut in and remind you and then would should cruise after that.

You do have to press your "speak" button on the microphone which sets up this little red light. So don't forget to do that and, unless you want people to hear all the little whispered comments that you make during the rest of the meeting, don't forget to hit the button and turn it off.

Secondly, the way that I will know who wants to talk is if you could just raise your hand. Then Kimberly Topper, our Executive Secretary, will take your names down and we will try to get to you in order. It is not a pure first-come-first-served basis in that we may call on people first who maybe have to leave or may not have expressed their viewpoint prior to that. So don't be upset if it

seems like we are not calling on you in the exact order that you raised your hand.

That being said, there are sometimes visibility problems. If you find that I am persistently not recognizing you, then say something at some point because, last meeting, for example, we had somebody over there who kept raising his hand. I couldn't see him and that was a problem that I had to correct about halfway through the meeting. So let me know if that seems to be the case.

In terms of the nature of our discussion today, for the people, again, around the table, I want to emphasize a few aspects of our goals for today. What we are trying to do today is to try to define some of these problems, shed light on some of the issues that have been raised and bring to bear some of the scientific and clinical knowledge and experience that will help illuminate these issues.

What we are not trying to necessarily do today is come to any consensus about anything. That would seem to be premature before we have fully defined the problem and I wouldn't want to stifle discussion by any efforts to reach a

premature consensus.

So disagreements are fine. I will encourage minority points of view. We want to, again, bring out all the relevant points for discussion here before we seek towards achieving consensus. Of course, if we achieve consensus, that is fine but that is not the primary goal so don't be afraid to bring out countervailing points of view.

So, with that, I will introduce Kimberly Topper, our Executive Secretary, who will read the conflict of interest statement.

Conflict of Interest Statement

MS. TOPPER: The Food and Drug Administration has prepared general matters waivers for the following special government employees who are participating in today's meeting of the Anesthetic and Life Support Drugs Advisory Committee Meeting being held by the Center for Drug Evaluation and Research for Dr. Nathaniel Katz, Dr. Vera Bril, Dr. Michael Ashburn, Dr. Solomon Aronson and Dr. Robert Dworkin.

The waivers permit them to participate in the committee's discussion of specific issues in the development of pharmaceuticals for the

treatment of neuropathy and neuropathic pain. Areas for discussion will include the duration of clinical trials, evaluation of nerve function, evaluation of electrophysiological endpoints, appropriate clinical endpoints and appropriateness of general and specific claims.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

Unlike issues before a committee in which a particular product is being discussed, issues of broader applicability such as today's meeting involve many industrial sponsors and academic institutions. The committee members have been screened for their financial interests as they apply to the general topic at hand. However, because general topics impact so many institutions, it is not prudent to recite all potential conflicts as they apply to each member.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited guests, we

would like to disclose that Drs. Peter Dyck, David Cornblath, John Farrar, Thomas Foster, Michael Polydefkis, Mark Rendell, Michael Rowbothom, Stephen Shafer and Clifford Woolf have reported financial interest in firms which may be affected by the committee's discussion.

Dr. Dyke reported that he has received honoraria and grant support from Asta Medica and Eli Lilly over the past three years. Dr. Cornblath reports that he has been involved in clinical trials supported by Pfizer and Wyeth-Ayerst. He has been a consultant to Asta Medica, Vertex Pharmaceuticals, R. W. Johnson and Pfizer. He has also been a member of the Schwarz Biosciences Data Safety Monitor Board.

Dr. Farrar reports that he has been a consultant to Endo Pharmaceuticals and has been involved in Pfizer-supported research. Dr. Foster reports that he owns stock in Johnson & Johnson and Pfizer. Dr. Polydefkis reports that he has received research support from Pfizer Pharmaceuticals and Johnson & Johnson. He has also received consulting fees from Johnson & Johnson.

Dr. Rendell reports that he is a principal investigator on many studies and does studies on

many neuropathic drugs. Dr. Rowbothom reports that he is a researcher on Pfizer and Johnson & Johnson-supported studies and has an Endo Pharmaceuticals study pending. He also receives consulting fees from End Pharmaceuticals.

Dr. Safer reports that he does consulting for Ethicon-Endo Surgical Division of Johnson & Johnson. Dr. Woolf reports that he is the principal investigator on Pfizer and Pharmacia-sponsored studies and he receives consulting fees from Pfizer, Pharmacia, Endo Pharmaceuticals and Wyeth. In addition, Dr. Woolf receives speaker fees from Pfizer and Pharmacia.

In addition, we would like to note for the record that Dr. Charlie McLesky is participating in this meeting as an industry representative acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

In the event the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants,

we ask, in the interest of fairness, that they address any current and previous involvement with any firm whose products could be affected by the committee's decision.

Thank you.

DR. KATZ: Thank you.

Introductions

What I would like to do now is to go around the table and do introductions just so we can get to know each other and to help facilitate our efforts together today. So if we could just go around the table and if everybody could take 30 seconds and let us know who you are, where you are from, what you do and what your role is with respect to neuropathy and neuropathic pain.

Why don't we start at that end of the table, please.

DR. McCORMICK: Hi. I'm Cynthia McCormick, FDA. I am the Director of the Division of Anesthetic, Critical Care and Addiction Drug Products.

DR. RAPPAPORT: Good morning. I am Bob Rappaport. I am the Deputy Director of the Division of Anesthetic, Critical Care and Addiction Drug Products at the FDA.

DR. HERTZ: Hi. I'm Sharon Hertz. I am also with the FDA, the same division. I am a medical reviewer.

DR. DAL PAN: I am Gerald Dal Pan. I am a medical reviewer in the same division at FDA.

DR. McLESKY: I am Charlie McLesky. I work for Abbott Labs today representing industry.

DR. FOSTER: Thomas Foster, Professor of Pharmacy and Anesthesiology at the Colleges of Pharmacy and Medicine, the University of Kentucky Medical Center, Lexington, Kentucky. I am the consumer representative.

MS. DELPH: Yvette Delph. I am patient representative from the HIV community, Silver Spring, Maryland.

DR. ASHBURN: I am Michael Ashburn. I am Professor of Anesthesiology at the University of Utah. I am Medical Director of Pain Programs at Primary Children's Medical Center and at the University of Utah.

DR. BITETTI: I am Janice Bitetti. I am with the Department of Anesthesia and Critical Care at George Washington University and I am one of the committee members.

DR. SHAFER: Steve Shafer. Despite what

it says here, my primary appointment is Professor of Anesthesia at Stanford University, Adjunct Professor of Biopharmaceutical Science at UCSF and I am here for both anesthesia and clinical pharmacology.

DR. BRIL: I am Vera Bril. I am a neurologist from Toronto. I am a consultant to the FDA. I am interested in clinical trials of diabetic neuropathy and various other neuropathies and neuromuscular disorders.

DR. DWORKIN: I am Bob Dworkin, Professor of Anesthesiology and Neurology at the University of Rochester School of Medicine.

DR. ROWBOTHOM: Michael Rowbothom, Professor of Clinical Neurology and Anesthesia, University of California, San Francisco.

DR. POLYDEFKIS: Michael Polydefkis. I am a neurologist at Johns Hopkins and I am interested in the use of skin biopsy in diabetic neuropathy and in clinical trials.

DR. RENDELL: Dr. Rendell. Mark Rendell. I am Director of the Diabetes Center at Creighton University. I am interested in diabetic neuropathy.

DR. WLODY: I am David Wlody. I am an

Associate Professor of Anesthesiology at the State University of New York, Downstate Medical Center.

DR. FARRAR: I am John Farrar. I am a neurologist with appointments in the Department of Neurology, Anesthesia and Epidemiology at the University of Pennsylvania. My interest is in the design and methodology of analysis for clinical trials of pain, in particular neuropathic but also somatic pain.

DR. CORNBLATH: Hi. I'm David Cornblath. I am a neurologist at Johns Hopkins. I have been interested in electrophysiology and nerve conduction in clinical trials.

DR. WOOLF: I am Clifford Woolf, Professor of Anesthesia Research at Harvard Medical School and Massachusetts General Hospital. I am interested in pain mechanisms and its application to new clinical outcome measures.

DR. KATZ: Thank you.

With that, let's have introductory comments from Dr. McCormick.

Welcome

DR. McCORMICK: Thank you. Dr. Chairman, committee members, invited guests, members of the FDA and members of the public, welcome to today's

meeting of the Anesthetic and Life Support Drugs Advisory Committee to discuss issues surrounding the development of drugs for peripheral neuropathy and to treat neuropathic pain.

This meeting has been convened to provide an opportunity for the FDA to gain advice from its distinguished advisors and experts in the area of neuropathy and neuropathic pain on issues that will enable the FDA to provide guidance for industry to develop solid programs that will ultimately support the approval of new pharmacotherapies for these conditions.

There are currently over forty agents in various stages of development for the treatment of neuropathy and neuropathic pain. Along with the pharmaceutical industry, we face many challenges in the development of drugs for these conditions. For example, there is little history or precedent of drugs demonstrated to be successful to treat peripheral neuropathy.

The course of many neuropathies such as diabetic polyneuropathy is slow and others variable and this must be factored into the duration of trials, particularly if the agent under evaluation is anticipated to slow the course of the

neuropathy.

To perform clinical trials of several years duration may be a huge undertaking for industry and should be embarked upon with the best information on the most relevant outcomes and best analysis methods in hand to deal with the inevitable problems that we will see; for example, high dropout rates.

The definition of an outcome that is clinically meaningful to patients may be disputed. The tools used to measure outcomes are abundant and choosing the most appropriate is a challenge. The role of objective measures of nerve structure and function such as biopsies, electrophysiologic testing and quantitative sensory testing may have a role but should be placed in an appropriate context relative to clinical outcome, either as a supportive role or potentially as a surrogate marker if appropriate validation exists. We will be discussing some of these today.

As in any rational drug-development program, attention should be given to the projected target population or populations and should neither be too broad nor too narrow as this will ultimately be reflected back in the labeling for the product

once it is approved.

Ideally, the characteristics of that population should be described in the label. Attempts to acquire broad marketing claims from large open-label safety studies gained in populations not relevant to the identified target population will likely not gain inclusion in the label.

The populations studied in Phase III efficacy trials is too narrow. Labeling that is overly narrow may result. While that may not affect how the drug is used in real practice, it will affect how it can be advertised, something of importance to industry. In that context, there is also the potential that the important safety information is not collected in the most relevant populations.

Turning to neuropathic pain, today's focus will solely be on pharmacologic therapy for neuropathic pain recognizing that there is a also a role for non-pure-pharmacologic approaches such as nerve block, dorsal-horn stimulation and so on.

There are only two drugs that are currently approved for pain associated with neuropathy, carbamazepine, initially approved in

1968 for epilepsy and later gained an indication for trigeminal neuralgia and Lidoderm patch approved in 1999 for postherpetic neuralgia.

Quite a large number of medications are currently under development for the treatment of the symptoms associated with postherpetic neuralgia as well as for the treatment of pain of neuropathic origin associated with many diverse etiologies. For these agents, we need to understand whether there is consensus on what outcomes are clinically meaningful, what measures are best to describe them.

To what extent should specific characteristics of neuropathic pain such as static and dynamic allodynia, pain descriptors, spontaneous pain and so forth be assessed.

One of the most challenging questions from a regulatory standpoint is the whole issue of the extent to which the success of a new agent in one neuropathy or disorder manifested by neuropathic pain can be extrapolated to a second or a third or, even more generally, is the state of knowledge advanced sufficiently to be able to consider a general claim for neuropathic pain. If so, what should be the criteria; common mechanisms of drug,

common underlying mechanisms of disease, PK-PD modeling considerations, some other thoughtful or reproducible criterion or some have proposed simply an arbitrary number of replicated trials.

These are the things that we are struggling with on a daily basis. It is our hope today that we may hear the thoughts from the committee on some of these areas. The questions that have been formally submitted to us from industry have been incorporated into the questions that we have brought forth for the committee or, in other cases, you will hear from the FDA speakers. It is important to have adequate consideration for these.

Today, you will be hearing from the FDA staff of the Division of Anesthetic, Critical Care and Addiction Drug Products to give you the regulatory context for today's discussion. We have asked several of the guest speakers to speak on selected topics that will, hopefully, stimulate discussion surrounding questions about quantitative measurements, of nerve function, confirmatory measures in clinical trials, discussion of neuropathy scales which are most appropriate for clinical drug trials.

This afternoon, we will hear a point-counterpoint discussion on the issue of general versus individual claims for pain associated with neuropathy, the lumping versus splitting debate.

We hope to gain new insights from the discussions of the committee today viewing it as a starting point, applying what we learn from today's meeting to the first steps of developing a guidance for industry.

Thank you and welcome.

DR. KATZ: Thank you, Dr. McCormick.

What we will go to next is the open public hearing. As most of you know, members of the general public are invited to share their thoughts and comments with us as part of these committee meetings. One member of the general public has requested time and that is Dr. Najib Babul. Dr. Babul, you could step to the podium, please. You have got ten minutes to share your thoughts with us.

Open Public Hearing

DR. BABUL: Good morning, Dr. McCormick, Dr. Katz, FDA and members of the advisory committee.

[Slide.]

My name is Najib Babul. I am the Chief Scientific Officer of TheraQuest Biosciences based in Blue Bell, Pennsylvania. I am here because of a keen interest in analgesic drug development including neuropathic pain. I would like to address the committee on the issue of analgesic drug development for neuropathic pain specifically some of the methodologic issues that we have been struggling with.

[Slide.]

At the present time, the regulatory framework for development of analgesics is actually fairly limited. We have the 1992 guidelines. These guidelines are directed primarily at single-dose evaluation of analgesics in acute pain. They say virtually nothing with respect to the evaluation of drugs for chronic pain or with respect to the evaluation of drugs for neuropathic pain.

More recently, the CPMP has issued a draft guidance document on evaluation of analgesics for pain. These guidelines, too, although more recent, don't provide substantive support and direction to drug developers and, in my opinion, to regulators

for chronic pain and for neuropathic pain as well.

[Slide.]

We also have a number of supportive guidelines, both from the CPMP and from the FDA. I would argue that if we look at the osteoarthritis guidance document, while directed at a more mature discipline, may represent a basis for some long-term approach by the agency for guidelines development in neuropathic pain.

[Slide.]

What is the regulatory framework for approval of drugs for neuropathic pain? Put another way, should a sponsor be able to obtain a broad indication for neuropathic pain or is it necessary to replicate evidence of efficacy for each neuropathic-pain state. This is an issue that a number of us have been struggling with and I know that the division, likewise, has been considering this issue.

[Slide.]

Let's look at the pros and cons on this issue. I certainly will not be able to do a kind of justice that speakers later on who have a bit more time will be able to do, but let me just review this issue by saying that proponents of a

broad indication for approval for neuropathic pain would argue that the response is often generalizable, that pivotal studies in several pain states should be adequate for a broad claim, that if we require a sponsor to replicate evidence in every neuropathic-pain state that this will push developers to a minimalist approach to development getting a very narrow indication with the attendant off-label use of the drug.

Consequently, some would argue that many painful neuropathies may remain orphaned. People who support the view that we ought to look at this on a subindication, if you will by a subindication basis, would argue that the etiology, presentation and natural course of these neuropathies is different, that the mechanisms of pain are frequently different, that replication is, indeed, essential in order to avoid erroneous chance findings, and we have seen some in the literature, to be sure, and that, quite to the contrary, failure to require studies in each painful neuropathy may, itself, result in orphaning of specific neuropathies

[Slide.]

I think it will come as no surprise to Dr.

McCormick and Dr. Rappaport that I would make a case for a broad neuropathic claims structure.

[Slide.]

But, before we do that, we need to make sure that we have our operational definitions in order because when we are talking about neuropathic pain, it conjures up different things to different individuals.

Are we talking about peripheral neuropathies? Are we talking about phantom pain? Are we talking about complex regional-pain syndrome I or type II. Are we talking about nerve-root disorders, central pain or spinal-cord-injury pain. These are all different issues, different presentations and natural histories and we need to be certain that we are using the same terminology.

[Slide.]

If we drill it down further, just looking at peripheral neuropathic pain and, again, to buttress the point that a subindication-by-subindication claim would be very difficult, we have a wide variety of clinical presentations. We have patients with traumatic mononeuropathies which could range from entrapment neuropathies to transection to causalgia to stump

pain and post-thoracotomy pain to other mononeuropathies and multiple mononeuropathies including diabetic and postherpetic neuralgia and trigeminal neuralgia and, of course, a series of polyneuropathies of varying etiology from nutritional and metabolic to drug-induced, each one with a somewhat different mechanism, to hereditary polyneuropathies and neuropathies secondary to malignancy.

[Slide.]

I hope this is not a rhetorical question, but the question I would have is will we ever get drugs approved for neuropathic pain or at least a broad indication of neuropathic pain if there is a requirement for replicate evidence in each painful neuropathy.

[Slide.]

To compound the issue further, when we are talking about neuropathic pain, we are not just dealing with neuropathic pain of noncancer origin. Indeed, in a series of randomized clinical trials that we have been doing for the last fifteen years, we have attempted to systematically stage the patient's pain characteristics. This slide shows data from four specific studies where anywhere from

2 to 12 percent of patients had solely neuropathic pain or primarily neuropathic pain as their reporting symptom.

In terms of contributory neuropathic pain, anywhere from 9 to 45 percent of patients had some contributory neuropathic-pain component. So it is certainly a complex challenge for drug developers.

[Slide.]

One of the questions that we ask ourselves is whether there is a wide divergence in efficacy response to various pharmacologic agents in painful neuropathies. I would suggest that if the answer is yes, that there is wide divergence, then a broad claim may not be possible. If the answer is no, then, clearly, a broad claim may be possible.

What is the evidence for a comparable response across painful neuropathies?

[Slide.]

We recently completed a retrospective evaluation of the literature looking at randomized double-blind placebo-controlled studies, looking only at orally administered drugs that were given for at least four weeks duration. We restricted our evaluation only to studies in the public domain involving postherpetic neuralgia and diabetic

neuropathy given that there is a fair bit of evidence in those two neuropathies.

We looked at baseline and final endpoint scores and attempted to calculate an overall response by subtracting the placebo response which, in general, was anywhere from 30 to 50 percent of the overall response from the drug response.

[Slide.]

What I have here is a slide with the data on diabetic neuropathy. As you can see, a series of agents including amitriptyline, desipramine, gabapentin, pregabalin, limotrigine, mexiletine, tramadol, oxycodone and dextromethorphan show a fairly robust response in diabetic neuropathy.

There are some missing data here because we were unable to obtain baseline data in some cases and there was a carryover effect in a number of crossover studies. In the case of limotrigine, there is also data in HIV neuropathy and in central pain although there is inconsistent data in spinal-cord-injury pain and mixed polyneuropathy.

[Slide.]

If we look at postherpetic neuralgia, we find that, at least for a number of commonly used drugs including amitriptyline, desipramine,

gabapentin, pregabalin and oxycodone, there is also a similar robust pharmacologic response almost of comparable effect size within the variability we expect from study to study.

These data would suggest, at least to me, that it should be possible, within a preponderance of evidence, to generalize and obtain a broad neuropathic-pain claim.

[Slide.]

One of the other issues that we have been struggling with is what it is that we need to measure in neuropathic-pain studies.

[Slide.]

In a study that Peter Watson and I did in and published in Neurology in 1998, we systematically looked at this issue. Mitchell Max and others have done this as well.
Almost all patients, 97 percent of the patients, had ongoing or steady pain and about 90 percent of patients had brief pain and evoked pain described by a variety of different descriptors.

[Slide.]

If you look at the specific pain characteristics, certainly in terms of peripheral neuropathies, steady pain, paroxysmal pain and

allodynia are fairly common features. These patients often have some sensory impairment as well. Certainly these are some of the things we ought to look at in all randomized clinical trials in neuropathic pain.

[Slide.]

These are data from a randomized placebo-controlled clinical trial we did with oxycodone, in this case, OxiContin, looking at these three dimensions of pain, steady pain, paroxysmal pain and allodynia. On all three dimensions, we found a fairly robust pharmacologic response for oxycodone.

These data are not unique to oxycodone or to opioids. The have been shown with meprotalin, amitriptyline, desipramine and a number of other pharmacologic agents.

[Slide.]

The other issue is what else should we be measuring. Clearly, as Dr. McCormick suggested, the durability of the response needs to be measured. My presentation here largely deals with symptom relief. I am not here to speak to the issue of disease progression and the subset of agents that are being looked at in terms of

disease-modifying agents, but the durability of efficacy response is an important issue given that these patients are going to be on treatment for a long period of time.

Quality of life and function are also important issues. The role of quantitative sensory testing certainly is something that is the subject of some debate. One of the issues that I would put to the division and to the advisory board is if you find a significant difference or a positive finding on electrophysiologic testing and find no actual subjective benefit, what does that mean?

If, on the other hand, you find a negative finding on objective electrophysiologic testing and find a positive finding on the subjective findings, what does that mean? In other words, I am not entirely certain that, other than in an exploratory or mechanistic sense, that this adds much to the labeling, itself.

Finally, if we are looking at centrally acting drugs, as we often are, we need to consider neuropsychological and cognitive effects of these drugs.

[Slide.]

This is my last slide. I would like to

just briefly suggest to you, at the cost of being somewhat prescriptive because I think this is where the rubber meets the road, as to what a core development program could look like for a 505(b)(1) drug for a broad neuropathic-pain indication.

I would suggest that one of the things that is lacking uniformly with a range of pharmacologic agents across therapeutic agents and divisions is proper dose-finding studies. So I think it is important that dose-finding and dose-frequency-finding studies be conducted in at least two painful neuropathies. However, these studies probably can be incorporated into pivotal clinical trials.

In addition, I would suggest that replicate evidence of twelve-week efficacy, which is a standard that I think most of us, including the division, have accepted in chronic pain of noncancer origin, replicate evidence of twelve-week efficacy in postherpetic neuralgia combined with replicate evidence of twelve-week efficacy in diabetic neuropathy ought to be a sufficient basis for a broad neuropathic claim.

I think, however, if the division should take such an approach, sponsors should be given

some latitude in terms of drug development. Perhaps robust response in twelve-week efficacy studies in two separate painful peripheral neuropathies plus one or two other models such as central pain, spinal-cord pain, complex regional-pain syndrome, nerve-root pain, et cetera, might be adequate as a basis for a broad indication.

I think cognitive impairment, both acutely and chronically, need to be evaluated. Obviously, there is a need for long-term safety data. Finally, the clinical pharmacologic section of the label should reflect the efficacy data, the precise studies in which the drug has been found to be effective, ineffective, the magnitude of the pharmacologic response and, indeed, the specific pain dimensions that have shown a positive response.

Thank you.

DR. KATZ: Thank you, Dr. Babul. Stay there for one second.

Does anybody around the table have any questions for Dr. Babul based on the information he has just presented?

DR. KATZ: Dr. Farrar?

DR. FARRAR: I was interested in knowing, with the effect-size slide that you showed, you had subtracted out the placebo rates. I am not quite sure how you calculated an effect size. Was it the remaining effect size?

DR. BABUL: That's correct. What we did is we took the baseline value, subtracted the final endpoint value from that to come up with the effect of the test drug, did the same thing for the reference drug and then subtracted one from the other.

In general, what we found is the placebo response was about the same as what we see in osteoarthritis, for instance.

DR. FARRAR: If I could follow up. The effect size was presented as a percent. I am wondering, a percent of what?

DR. BABUL: That was a percent of the baseline value in terms of percent reduction of baseline value, probably more appropriately labeled as response rather than effect size.

DR. KATZ: Dr. Woolf?

DR. WOOLF: You used that same slide to argue the case that different drugs had similar degrees of efficacy. But your desipramine had

about a 10 percent effect in diabetic neuropathy and over 30 percent in postherpetic neuralgia. That, obviously, could be by chance but it does raise the issue that there may be differences in efficacy between different conditions.

DR. BABUL: You are quite correct. Let me make a couple of points in that respect. The first is that I think most of us have accepted, although not all, that a minimum clinically perceptible difference is about 10 percent and some have argued perhaps 15 percent.

So, in that sense, I think that most clinicians agree that desipramine provides a reasonable response in postherpetic neuralgia and in diabetic neuropathy. I think part of the challenge here is that a number of studies did not lend themselves to calculating a pharmacologic response because of the absence of baseline values.

Without a doubt, there are some differences which, perhaps, would argue for replication. My point is that replication may be reasonable. Certainly, there is a sound foundation for replication at the agency although arguments have been made for large single studies as well. But replication in all neuropathies may be

challenging.

The other point I would make is that mechanistically, within a given neuropathy, there are substantial differences. So, if we start looking at diabetic neuropathy, there are mechanistic differences in terms of presentation of patients within a given neuropathy so where, exactly, does this process end?

There are also other differences. I talked about lamotrigine in terms of some variability where in certain states, like HIV neuropathy, the findings are positive. In central pain, they are positive. There are no data on postherpetic neuralgia, unfortunately, that I am aware of but we know that in a recent study published in Pain, in spinal-cord injury pain, the results were negative and in mixed neuropathy the results were negative.

So it always hard to know whether it is the design, a function of dose, whether it is a question of polypharmacy, appropriateness or washout, the instruments that are being used and I think there is probably a need for standardization.

DR. DAL PAN: Any other questions? Dr. Shafer?

DR. SHAFER: Our pain group at Stanford feels fairly strongly that VAS scores for chronic pain can be very hard to interpret and primarily push for quality-of-life indicators. But, in your presentation here, talking about postherpetic neuralgia, at least what I am inferring from your presentation is you see VAS as being more the primary endpoint and things like quality of life being potentially secondary endpoints on the studies.

Is that a correct interpretation of your experience and where you are directing this?

DR. BABUL: In the literature, a majority of investigators have used either a visual-analogue scale or a categorical scale for evaluating pain as a cardinal feature. Most studies have not looked at various dimensions of pain. To be sure, people have--Mike Rowbothom and others have employed the McGill Pain Questionnaire with the various descriptors that that provides, but most people have not specifically targeted at each visit specific dimensions of pain.

But a majority of people have used the visual-analogue scale. There is this separate issue about what constitutes a win. This is an

ongoing struggle. Drug developers concerned about coprimaries--in other words, a requirement that a win be based not just on pain but on quality of life. Some would argue function or return to work which is a rather daunting task.

I think many of us who are involved with pain management feel that pain relief alone is a reasonable endpoint. Certainly, we hope that that translates into quality of life. There is not a huge amount of work done in terms of quality-of-life instruments in neuropathic pain although there is some literature out there.

DR. SHAFER: Just to quickly follow up, part of the distinction was acute- versus chronic-pain syndromes. Do you see any bifurcation between the measures for acute and the measures for chronic?

DR. BABUL: In both acute pain and in chronic pain, in chronic pain as it relates to, say, osteoarthritis, myofascial pain, cancer pain, any neuropathic pain, both categorical and visual-analogue scales have shown validity and actually fairly good reliability. Unfortunately, VAS seems to be something that most investigators and academics seem to prefer and I think most

patients probably prefer some sort of a numerical or categorical scale and there is this challenge. But both in acute and chronic pain, we have used VAS successfully.

DR. KATZ: Thank you.

Dr. Farrar?

DR. FARRAR: Just two quick comments. One is the minimal perceptible difference is clearly a different measure than a clinically important difference and the second is that, to try and conclude something from the graphs that you have here, it is very important to remember that these measures are looking at the mean value and that the mean value is not a unique answer to the question of how many people actually got better.

You can come up with any of a number of different interpretations and I would be interested if any of these studies actually published something about the number of patients who actually got better to try and look at some of that data as well.

DR. BABUL: Dr. Farrar, I would certainly approach this issue with some trepidation in your presence, but let me suggest that, from a number-needed-to-treat basis, there are generally

consistent findings as well for most of these pharmacologic agents with some discrepancy that you would expect across clinical trials.

DR. KATZ: Thank you, Dr. Babul. We appreciate your comments.

We do have a little bit of time left in the Open Public Forum so if there is anybody in the room who would care to come up and share some thoughts with us about these issues, you are welcome to do so at this time. Just approach the center mike right up front.

I feel like I have a clean conscience that everyone has been offered an opportunity. We will go on with the rest of the program, then.

Next, we will have a number of presentations from the FDA folks on some of the regulatory issues in this area beginning with Dr. Sharon Hertz.

FDA Presentations

General Clinical/Regulatory Issues in Development of Drugs Intended for Treatment of a Chronic Illness

DR. HERTZ: Good morning.

[Slide.]

I am going to discuss the general

regulatory issues that are involved in drug development in general so that we can think of them as we discuss neuropathies specifically. The general regulatory framework in which we work here at the agency compels us to keep the entire drug-development process in mind when we review all submissions. This extends from the time of the initial application to study the drug in humans, the IND submission, to the time when the product will be considered for marketing at the submission of the New Drug Application, or NDA.

Clinical drug development plans and NDAs are reviewed for efficacy in the context of the drug safety profile. At the same time, the choice of clinical-trial design and study populations are considered for the future promotional and marketing implications.

The clinical trials used to support an NDA are the basis for the drug's indication and will be reflected in the language of the product label. Marketing and promotional claims are based on the information in that label. This last point is important and I will refer to it later at the end of my talk.

[Slide.]

Basically, a company has a hypothesis that Drug A is capable of treating a symptom or a disease in a safe and effective manner. The proof is at least two adequate and well-controlled trials demonstrating this hypothesis to be true with additional safety information as needed. The results, hopefully, are approval of the product and a label. Then the product will be promoted based on the findings of efficacy.

[Slide.]

So what is the regulatory basis for studies in support of efficacy? What is the regulatory basis for the requirements of the safety database? And how are these findings, the product label and promotion related?

[Slide.]

The legal standard requiring the demonstration of effectiveness was added to the Food, Drug and Cosmetic Act in 1962. It states that no person shall introduce, deliver for introduction, into interstate commerce any new drug which basically hasn't been shown to be effective.

[Slide.]

The regulations also state that full reports of these investigations which support the

demonstration of efficacy must be submitted to the application and that a finding of substantial evidence that the drug will have the purported effect in the intended conditions of use must also be provided to support approval for the application.

[Slide.]

The regulations also describe the term substantial evidence that is necessary in support of a finding of efficacy. Substantial evidence is defined as evidence consisting of adequate and well-controlled studies by experts qualified to perform those studies so that the studies can be the basis to conclude the drug will have the effect purported.

The term "adequate and well-controlled investigations" was taken by the agency to mean at least two adequate and well-controlled trials.

[Slide.]

The Code of Federal Regulations describes the essential characteristics of an adequate and well-controlled trial. This includes the required documentation of planning, conduct, data handling and record keeping. The purpose of conducting these clinical investigations is to distinguish the

effect of the drug from other influences such as spontaneous change within the course of the disease, placebo effect or biased observation.

Additional, the Regulations describe the types of study designs that permit what is considered a valid comparison using a control to provide quantitative assessment of drug effect. This section also describes the use of concurrent placebo control or dose-comparison controls or the use of objective measures when available and a placebo effect is expected to be negligible.

Concurrent acting controls are described along with the potential pit fall for a lack of assay sensitivity if not used with other types of controls.

[Slide.]

There is some flexibility with respect to the number of trials required for approval based on the situation and the availability of other supportive data according to the FDA Modernization Act.

The legal and scientific bases for the quality and quantity of evidence necessary to support effectiveness are summarized in a guidance. I just want to say that the requirement for more

than one adequate and well-controlled study doesn't reflect so much the need to replicate findings in the same type of study but more the need to provide independent substantiation of experimental results.

The intent is to avoid unanticipated bias or chance results and to demonstrate the findings are generalizable to patients under different conditions.

[Slide.]

The finding of safety is more accurately the finding of acceptable risk in the context of the efficacy of the drug. The requirements for the safety database for drugs intended for chronic administration are also described in a guidance.

[Slide.]

The finding of effectiveness is then reflected in the product label in pertinent sections, particularly indications and usage material must be supported by substantial evidence of effectiveness. Comparative statements about other products must also be supported by substantial evidence.

[Slide.]

Findings referable to safety are reflected in several sections of the label according to the

regulations and postmarketing information can be added as needed.

[Slide.]

Once the wording in the label is agreed upon and approved, the sponsor may advertise and promote the product in accordance with the regulations. The advertisements must be accurate and balanced and limited to the indications included in the label. This is a point that has been mentioned already and it is an important point for the following reasons.

First of all, a product that is effective for more than one indication may be effective under different conditions of use, different dosing regimens, so it is important that findings of efficacy be supported by data for that indication.

[Slide.]

It is also particularly important because a product that is used in different populations may have different safety profiles based on the characteristics of those populations so age, comorbidity, concomitant medications with potential for drug-drug interactions are all important features that need to be explored in an adequate safety database.

The one other feature why this is important is because it is necessary to set a level playing field where all companies are held to a comparable standard. So, for a company to promote their product for a specific indication, it is incumbent on them to demonstrate the effectiveness and safety for that indication.

That is not to say that a product cannot be used in a manner according to clinical judgment by any given physician, but the approval and promotion of drugs are regulated processes and the FDA is responsible for implementing those regulations.

[Slide.]

So as we discuss the approach to drug development for products to treat neuropathic pain and underlying neuropathies, please keep in mind how these different pieces, the clinical trials, the safety data, the product label and product promotion fit together.

Thank you.

DR. KATZ: Thank you, Dr. Hertz.

Any questions from around the table for Dr. Hertz? Dr. Farrar?

DR. FARRAR: The one area that the

guidelines don't really speak to is with regards to the size of the beneficial effect. I wonder if you could just comment on that.

DR. HERTZ: I hope we cover that somewhat today in the discussions. We struggle with statistically significant differences in effect size between the placebo group and the active treatment groups versus the concept of a clinically meaningful difference. That is going to be on the roster for discussion today, so we don't have an answer yet specifically in this area.

DR. KATZ: Other questions for Dr. Hertz? I have a question. It sounded like, and correct me if I am wrong, you were making the point that, in meeting this criterion of two adequate and well-controlled trials for a specific indication that the agency is more impressed by a pair of trials where one actually differs from the other in terms of details of study design, location where the trial was conducted, et cetera, et cetera, as opposed to what we sometimes see which is two replicate trials that truly are replicated, where the trial is exactly identical and you could combine them or split them and it is the same thing.

Am I hearing you correct? Is that how that issue is perceived?

DR. HERTZ: Yes, short answer, for the reason that you want to have a little bit more generalizability. Otherwise, it is basically one big trial separated by some other divider.

DR. KATZ: Thank you.

Dr. Woolf, please?

DR. WOOLF: In terms of indications, it wasn't clear whether you were talking about, in the context of this meeting, symptom, let's say acute versus chronic pain, or neuropathic pain or postherpetic neuralgia.

Is there a difference between indication as a symptom or as a disease syndrome?

DR. HERTZ: The indication is basically what the claim for efficacy is based on. So, if you are going to say that a product is capable of relieving the pain of diabetic neuropathy, then that is your indication, symptom relief. It could also be that your product is intended to slow the progression or reverse the changes associated with diabetic neuropathy and then that would be the indication.

So it is really defined by what you see

the product, what the company sees the product, capable of doing and capable of proving efficacious doing.

DR. KATZ: Other questions for Dr. Hertz?

Thank you very much. Next we will have Dr. Dal Pan from the FDA who will be speaking further about specific clinical and regulatory issues that arise.

Specific Clinical/Regulatory Issues

DR. DAL PAN: Good morning.

[Slide.]

We have just heard from Dr. Hertz about the clinical requirements for the development and regulatory approval of drugs to treat chronic disease. The basis of this is embodied in the substantial evidence requirement which states that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof. In other words, the drug has to do what the label says it does.

What does this mean, then, for drugs for peripheral neuropathy and for chronic neuropathic pain. The basic challenge for the agency, for the industry and for researchers is to operationalize

the substantial-evidence requirement into clinical-trial design and clinical-development planning for drugs to treat peripheral neuropathy and chronic neuropathic pain.

So I would like to take a little bit of time today and just present to you some of the specific examples in clinical-trial design and clinical-development planning that confront the industry and confront us when we meet with industry to go over trial design and development planning.

The examples are not so much today to get specific answers to specific questions or specific plans but rather to present to you the scope of the important issues that are facing us and to be followed later today by a discussion of what the scientific and clinical issues are and how we can best be informed about these issues so we can carry that into sound decision-making in the future.

[Slide.]

So let's start with the example of Company A. The company wants to develop a drug to slow or reverse the progression of diabetic polyneuropathy. So several issues come up here with regard to clinical-trial design.

One of the first issues is what is the

appropriate outcome measure or measures. Some of the challenges here are there is no regulatory precedent. No drugs have been approved for this indication and there aren't many large-scale trials to guide us or to inform us as to what the best outcome measures are.

Because diabetic polyneuropathy is a complex disease, the issue of a composite outcome versus a single-measure outcome comes up. There are many composite-measure outcomes in the literature and we have seen a lot of proposals to use such composite outcome measures.

An example of such a measure would be the Neuropathy Impairment Score, or NIS, of the lower limbs known as NIS(LL)+7. This is a composite clinical measure that looks at weakness, sensory loss, reflexes and electrophysiologic studies of motor and sensory nerves, heart rate variability and vibratory-detection threshold.

One of the challenges is defining the degree to which this composite measure or any composite measure, or any single measure, for that matter, really reflects what the clinically important effect of a drug to treat diabetic neuropathy really is. Closely related to what the

outcome measure is is something we have heard in some of the discussion already this morning; what is the magnitude of the effect size.

We are translating clinical issues into quantitative measures, be they measures of percentage of patients who respond by a given criteria or mean values on some numeric outcome. What is the scientific and clinical basis for determining how big an effect size should be? That is important because that, then, becomes the measure of the effectiveness of the drug and, from a practical point of view, it is important in trial design because it forms part of the basis for sample-size determination.

When we also look at this class of drugs, we want to distinguish between slowing progression versus arresting progression of disease versus actually reversing disease. This may have implications for what the outcome measure is. It may also have implications for the duration of the trial as well as the sample size.

We want to also consider what is the role of other testing such as electrophysiologic testing. Measures of nerve-conduction studies have been well documented in diabetic polyneuropathy as

measures of extent and severity of disease as well as change over time. To what degree can these measures serve as markers or surrogate markers of the important clinical effects we want the drug to be able to have.

If a drug is going to reverse or slow the progressive neuropathy, it may also have a beneficial effect on symptoms during the course of the disease and how can we capture this in the trial as well. So these are some of the challenges involved in drugs for slowing the progression of diabetic polyneuropathy.

[Slide.]

Let's turn now to a different scenario. Company B wants to develop a drug to treat chronic neuropathic pain due to diabetes. Several of the previous issues are important here as well. Again, we come back to the appropriate outcome measure or measures.

What is the role of pain intensity reduction? What is the role of pain relief. What is the role of function as an outcome. What is the role of quality of life as an outcome? Because neuropathic pain can vary from person to person, what is the role of characterizing different

symptoms such as allodynia, lancinating pain, burning pain and, again, for both composite measures and single effect measures, what is the magnitude of an effect that is clinically important and what is the basis for determining what that effect size is?

Because chronic diabetic neuropathic pain is a complication of a systemic disease, we want to also consider how to account for the role of potential confounders; for example, the severity of nerve dysfunction and the level of diabetic control during the trial, especially since those may actually impact the outcome of the trial. Finally, because it is chronic disease, we want to be able to assess the durability of the effect.

[Slide.]

My last example is a sponsor that wants to have a drug to treat both chronic painful diabetic neuropathy and postherpetic neuralgia. The central issue here is the degree to which data from one etiology of neuropathic pain can support data from another etiology of neuropathic pain and, more broadly, can results from these studies be generalizable to types of neuropathic pain not studied.

So I have tried to give you an overview here of some of the important issues that are facing us today. We have more talks on the agenda to address some of these issues in particular, and we have put forth a variety of questions to spark some discussion.

Thank you.

DR. KATZ: Thank you.

First, we have a new arrival at the table. Everyone else had to introduce themselves, so, in the interest of equal treatment, please introduce yourself.

DR. FELDMAN: My name is Eva Feldman. I am a Professor of Neurology at the University of Michigan and I also direct a juvenile diabetes research foundation center where we study complications of diabetes.

DR. KATZ: Thank you. For logistical reasons, what we will do now is have Dr. Cornblath speak on electrophysiologic tests used in the evaluation of peripheral neuropathy and neuropathy pain.

Oh; I'm sorry. My mistake. Any questions for Dr. Dal Pan before he steps down? Dr. Shafer?

DR. SHAFER: Just quickly one thought, or

question, rather. There are a number of issues that you allude to including things like sensitivity to covariate effects. These kinds of trials have other complications. Commonly, the data are right sensors. People drop out of the trials. Trying to separate out the inter- and intra-individual variability which you were referring to would try to distinguish effect size from the number of people who actually have any effect at all.

To what extent do you expect to see population approaches brought into the analysis of data in pain trials?

DR. DAL PAN: Population approaches; you mean by percent responders?

DR. SHAFER: Population approach is really where you have a model of intra- and inter-individual variability and are modeling those effects simultaneous with an overall model of effect including, actually, survival in the trial which allows you to account for right censoring of your data.

DR. DAL PAN: The issue of censoring has come up in a lot of pain trials. I would actually like the committee maybe just to address that later

this afternoon. I think that one of the issues that concerns us is differential dropout rates. People in placebo groups drop out because they are not getting pain relief and people in active treatment groups drop out because they are getting toxicity from the drug or can't tolerate it, even if they had, say, pain relief in a pain trial.

So I think that might be something interesting for the committee to address, how to handle that. It is something we have dealt with.

DR. SHAFER: For acute pain, there has been a lot of good work with population modeling. I haven't seen much in chronic pain.

DR. DAL PAN: I am not very familiar with that, either.

DR. KATZ: Other questions for Dr. Dal Pan? Dr. Bril?

DR. BRIL: Hi. One of the basic issues that I find confusing is in trials in diabetic neuropathy when we are trying to prevent progression. They are very difficult. And we know that the rate of progression really varies very much with glycemic control. And we know that we can improve control in a lot of people but we know we don't improve it in many people.

We know a lot of people are out there with poor control and those are the people who have more complications. Yet, in some of our long-term studies now we are designing, we are selecting for people whose control is as good as we can make it but we kind of exclude the population who may be at highest risk for the complication.

I am just wondering what the agency thinks about broadening the study population to include people who might benefit most from the interventions you may want to be using. It is a real problem, I think, and has implications for the generalizability of use if a drug ever was found effectiveness for diabetic neuropathy.

You would be saying it is in those who have fairly good control. This is something that really exercises my mind. I wonder what the agency thinks.

DR. DAL PAN: I think it is a good point. I think that it is important that the drug be studied in the patients who could benefit from it. At the same time, I think your point is also right that control of diabetes during the trial can confound the outcome. So that is why we have wanted some criterion in the beginning as to who

can enter.

It is not necessary to include only people with the best diabetic control. I think that is actually one of the questions we have for the committee later is about the entrance criteria for diabetics. So I think maybe we can have some discussion on that later by the committee.

DR. KATZ: Dr. Farrar?

DR. FARRAR: I think, actually, the question was targeted more at the issue of efficacy versus effectiveness. I think the question was that if you use a very selective population and are able to show an effect size of some magnitude, the question then becomes what about people who are likely, or perhaps even more likely, to benefit from them but because of other issues may have a different set of problems.

I think you are referring to a population that is not generally studied which are the people who have highly variable glucose control.

DR. BRIL: I am referring to the population where a lot of studies now have upper-limit cutoffs for glycosylated hemoglobins. Yet, there are still people who are out there with these levels in spite of all efforts to improve

their control and then the argument is said, well, these are noncompliant people anyway.

But, actually, they are not. They would be happy to be in a study. I don't think they should be dismissed. So the question is how do we incorporate them into long-term trials and not exclude them?

DR. DAL PAN: I think that is something that we would like the committee to discuss this afternoon, actually.

DR. KATZ: Dr. Foster next.

DR. FOSTER: A question along the same vein. In the introduction this morning, we learned that there are multiple agents in development now. I think if you parse them into disease-modifying agents versus palliative agents, the question comes in Dr. Hertz' presentation at the end, in advertising, as we fast forward to the end, does the agency consider plans for polypharmacy in this area where drugs would be, say, in a diabetic who is developing neuropathy where initially palliative agents would be placed, then prescribed with disease-modifying agents. Is there a plan to incorporate this type of multiple drug use into the design of clinical trials?

DR. DAL PAN: I am not aware of any plan for that right now. The disease is to slow or to reverse the progression of diabetic neuropathy. Studies are generally entering patients with earlier-stage disease so who haven't developed a lot of the severe complications such as this chronic neuropathic pain.

So, usually patients with severe chronic neuropathic pain are not entered into those studies. They are entered more into studies for palliation.

DR. KATZ: Dr. McCormick, did you care to amplify on that?

DR. McCORMICK: Sure. I think, in so far as these many drugs that are under development are all being developed by different sponsors, each may have its own intent. I think that there certainly is a precedent for having approval for adjunction therapy. That is something that would have to be studied but could potentially make it into a product label if it had been studied.

DR. KATZ: Dr. Woolf.

DR. WOOLF: You mentioned the complexity inherent in studying the progression of a chronic disease that may be changing. Some of those

changes may be associated with the mechanisms that may be responsible for the pain so that, early in the disease, the pain may be responsive to a particular pharmacological mechanism and later it may not be.

That needs the mechanisms to separate out the response of different patients according to where they are along the natural history of that disease.

DR. DAL PAN: I think you are right. I think we are going to have some discussion later today about mechanism-based selection of agents.

DR. KATZ: Are you suggesting, Dr. Woolf, that it may be important in clinical trials of neuropathic pain to categorize patients up front based on duration of disease among other things in order to, later on, look at subgroups of patients who may be more or less responsive based on their position in the natural history?

DR. WOOLF: We all recognize that some patients respond and others don't to the treatment. I think, certainly, one of the explanations would be that the symptoms that are being generated are reflecting different mechanisms which occur at different times in the disease course.

So, rather than always doing that post hoc, I think one of the ways is to try and define that up front.

DR. KATZ: Dr. Dworkin, then Dr. Rendell.

DR. DWORKIN: I was wondering, with respect to this issue of a broad indication versus specific indications, are there any precedents where the FDA has approved a drug in other areas of medicine for a broad indication based on controlled trials in several more specific diseases?

DR. DAL PAN: I frankly have to admit ignorance to answer that question. I can't answer you yes or no because I just don't have an example. Maybe one of my colleagues does.

DR. KATZ: Anybody else from FDA?

DR. McCORMICK: Actually, I think in the area of pain, there has been that precedent. We are currently examining that issue but that has been the precedent since about 1992.

DR. KATZ: Anyone else from FDA have any comments about the areas of medicine perhaps outside of pain where there is a precedent for providing broad labels after studies are done in specific subcategories? I wonder if acute pain, itself, might be an example of that where trials

are typically done, and correct me if I am wrong, in usually dental pain and some post-surgical model with a pair of controlled trials in each one and then the label is given for acute pain broadly despite the fact that there may be different types of acute pain that were not addressed in the program.

DR. McCORMICK: Right. That is what I was referring to.

DR. KATZ: Dr. Rendell?

DR. RENDELL: One of the greatest concerns that I have, having looked at most of the diabetic-neuropathy agents and having seen them fail on statistical grounds time and time again is that we are dealing with diabetic neuropathy as if it were a single disease as opposed to a condition with multiple different etiologies, the recognition that there may be certain subgroups of patients who may respond to a given agent and that subgroup of patients is not enough to sway the overall statistic in the favor of significance.

I have no answers, but I would like to throw out the consideration that we need to start making an effort to identify responders, subgroup responders, and try to decide what it is about them

that makes them respond to a given drug so that we might be able to offer these subgroups meaningful treatment although the overall response of a given drug, as David and I both know, having done this for years, is going to be negative when we look at the overall statistic.

So I throw that out as a challenge and certainly I have no ideas on how to do that.

DR. KATZ: It sounds like there are at least two implications from your comments. One is that the trials may be false negative in the sense that, while overall negative, they may fail to identify, indeed, an important effect in a subgroup that otherwise there is no specific technology for identifying.

Secondly, the splitting issue may become even more complicated than that. Even a medication that works for painful diabetic neuropathy in general may, in fact, indeed only works for a subgroup of yet those patients which makes the splitting debate even more complicated.

Dr. Farrar is first and then Dr. Shafer.

DR. FARRAR: Just a couple of comments. There are, actually, some design methods of getting at what you are talking about, one of which is

using an enriched population and there is, obviously, great concern about how one does that. But, for instance, if you are interested in studying if a tricyclic is effective in a particular group, you could take patients who were responsive already to a previous tricyclic, take them off an put them back on.

There are a lot of design problems with that and we don't need to get into it. The second thing is that there are some statistical issues one can look at to enhance the ability to find small populations that, in fact, respond. We can talk about those at some point later, too.

DR. DYKE: Dr. Shafer?

DR. SHAFER: Again, just in follow up, I am wondering if there is a role in the study design, potentially in the labeling, too, for exactly that kind of enrichment that Dr. Farrar is referring to. We often do things--like if we are interested in trying a sodium channel blocker, mexiletine, we will bring patients in and essentially give them a total-body beer block. We give them lidocaine and examine their acute response to it to see if they have an analgesic response and then, if they do, consider them a

reasonable candidate for sodium-channel blockade.

Or they could just be responsive to opioids, an acute trial in the clinic of I.V. opioids to see if they are going to respond before trying them long-term of opioid maintenance. Is there a role in the process and, potentially, in the labeling as well for enriching it on a mechanistic basis, to say that the patients will first be shown responsive to this class of compounds.

DR. KATZ: Dr. Dal Pan, any comments on the issue of the regulatory issues for enriched enrollment trials?

DR. DAL PAN: First I would like to say that some of the things that have been brought up here about identifying who the drug is affective, and which subgroups may respond, a lot of that is what Phase II of drug development is about. It is about defining and characterizing the effect of the drug.

Then we traditionally call, then, Phase III, the confirmation of that finding. So I think what some of the committee members here have really done is distinguish between what should be done in Phase II and what should be done in Phase III. You

don't just start with an hypothesis and jump into a confirmatory trial. There is some not only dose-finding but also some hypothesis-testing of what the range of what the range of effects of the drug could be including in specific subpopulations.

So I think that is a lot of what is going on here. With regard to specific labeling, maybe one of my colleagues could answer. If we could actually put something in the label about what Dr. Shafer was mentioning, the patient may be responsive to Drug X if they respond to an I.V. opioid, for example.

DR. McCORMICK: First let me just say that what you have just described as the ideal in Phase II development is an ideal. It is something that we often don't see bear fruit in Phase III so frequently we aren't able to really identify the real responders and parse them out of the clinical trials.

But, if we were, if we had a mechanism to identify responders and if it was adequately studied, then we certainly would consider how that would find its way to the label.

DR. KATZ: Other comments from FDA folks on the regulatory implications of enriched

enrollment designs?

Thank you, Dr. Dal Pan, very much. Why don't we then go on to Dr. Cornblath. I'm sorry; one question, Dr. Rowbothom?

DR. ROWBOTHOM: I was just going to make one comment about study designs using some kind of a potentially predictive test. I have had a number of discussions with various pharmaceutical companies about Phase II studies that use things like I.V. lidocaine infusion or I.V. opioid infusions. Generally, there has been hesitancy to adopt those designs because of potential risks of the I.V. infusion, what do you do with patients who don't respond to the I.V. infusion, a number of other methodologic questions, plus there is very little published literature in that area.

So, although it is a very intriguing idea and the evidence that is available suggests that it would be a valid and successful approach, there is still very, very little data actually in the public domain that is available on that.

DR. KATZ: Thank you.

Without further ado, Dr. Cornblath.

Electrophysiologic Tests Used in the Evaluation of Peripheral Neuropathy and Neuropathic Pain

DR. CORNBLATH: Thank you.

[Slide.]

I would like to make three sort of opening comments. One, I would like to thank the organizers for asking me to come. It is a pleasure to be here. Two, I notice the chair next to me, Dr. Dyke, is not here. I think a lot of us in the room owe him a great gratitude of thanks for all the work that he has done over at the Mayo Clinic over many, many years. I will be quoting liberally from that.

The third is that I think there are still, and we will hear this from Michael and Eva, a lot of unresolved issues from the scientific standpoint here that are, if you will, separate from the industry issues but tie in very closely. Eva, I know, will be bringing up a number of these talking about these composite measures and particularly their use over time.

There is a document currently in preparation coming from the NIH to the Congress, I believe, on issues related to diabetic neuropathy and unresolved scientific issues that, if I am correct, Eva, should be available in the next months, should be out, and will highlight a number

of the issues that all of us are bringing up that are still ripe for funding from the NIH.

So, with that brief introduction, let me just say I am going to talk briefly on this topic. There is a lot written and what I have tried to do, basically, is boil it down to sort of a summary essence without a lot of data. Gerald and I talked about sort of what I was supposed to say.

[Slide.]

This is sort of the outline of what he told me I was supposed to say which is I was supposed to talk briefly about electrophysiologic tests, their natural history in diabetes, the correlation with outcomes, their use in clinical trials, a few practical issues and then I could give my own summary.

[Slide.]

So there are a number of electrophysiological tests available. I have changed the term briefly, as you will see here, to neurophysiological tests and, in fact, I saw Joe Arezzo, who is in the audience in the back, who is really a world-class expert in this. I hope he will correct me when I am wrong.

But there are a number of tests available

that can be used. I think one of the issues we keep hearing about is nerve conduction, nerve conduction, nerve conduction and, although that is the most studies and what I will spend most of the time talking about, you should be aware that there are a number of other testing modalities available. Not all have been as well studied but all are out there, all have been looked at to some extent in terms of reliability, validity and, in some cases, change over time.

The main ones that you hear about are sensory-motor-conduction studies and, in particular, as I will mention later from the Japanese, the use of F-waves in monitoring long-term electrophysiologic change in diabetic neuropathy, electromyography--that is, the actual placing of a needle in the muscle because that is viewed as minimally invasive, hasn't really been used much--although it is possible to do it, it hasn't been used much--quantitative sensory testing, and there are number of devices out there that can be used.

They are part of many of the composite measures that you will hear about from Eva and is a very nice and, i some cases, very simple highly

reproducible test that we shouldn't forget about.

Autonomic-function testing and QSART are, in my view, much more advanced. They require a degree of sophistication and expertise and don't yet have the longitudinal multicenter experience that I think we would like to bring these into clinical trials currently.

[Slide.]

The most comprehensive data we have in that we in the natural history of EDx studies in diabetes is longitudinal studies of a large number of diabetics who were tested very carefully using the Mayo measures which, again, are highly reproducible within their centers. They have published and studied over a long time.

As Eva will tell you, this is what is needed very dramatically with other measures and in other centers and in other populations. Some of that work is being proposed today. There is an enormous need to look at other measures in other populations over time. But this is the best data that we have and I won't read the little numbers up there. You can read them for yourselves. They are printed.

But the data is very solid that if you do

the NIS(LL)+7, you have highly competent people to do it, you are doing it at a center where essentially it was invented, you can show that there are these very precise changes over time and everybody from industry knows that you can then use these to say whether you want to, as was proposed earlier, show that you can slow the rate of progression, you can stop a disease of, in fact, you can improve a disease.

There are a lot of other measures that have been used. They all show the same thing; that is, a worsening over time. But none have the sort of extensive precision that the NIS(LL)+7 has.

[Slide.]

Again, the best data comes from Peter Dyke and his colleagues at Mayo. It essentially shows that nerve conductions, and, again, I am going back to nerve conductions, are clinically meaningful if you accept the statement, and it is hidden in there, that a two-point change in the neuropathy-impairment score is a clinically meaningful measure. Again, I don't know how many here are neurologists and have done this measure. Two points is, in my view, sort of right at the border of what probably two of us could get when we

are doing it based, side to side, the same patients.

But at least, when it is done by Mayo physicians at the Mayo Clinic, this is a very reliable number and it is equal to a precise change in nerve-conduction velocity of either a composite number of nerves or a single nerve or a change in the amplitude for either the composite nerves or single nerves.

So, if you can get the nerve conductions done, you can both look at amplitude and velocity in these motor nerves and you can show that they are equivalent to a change in the NIS score and two points on the NIS score is a significant clinical change.

[Slide.]

So where do we sort of stand? Again, this is summarizing a lot of data that is out there in terms of use, predominant, again, of nerve-conduction studies. They have been used forever. Probably the first one where it was used was, in fact, Eliason's study of diabetic rats where he made them diabetic and he could show that, in the diabetic rats, nerve conduction worsened compared to the controls. That was, I guess, in

the 50s. Since that time, nerve conductions have been used time and time again, either primarily or secondarily in this.

They clearly have shown in diabetes an improvement when the change in the diabetic case is very dramatic; the introduction in insulin therapy, the introduction of pumps, or dramatic treatment in children.

The third one is the one that has bothered everybody. Mark has already mentioned it. All the drugs have failed. Therefore, "all the composite measures have failed." One of the difficult questions that I think all of us around the table are asked constantly from industry which is, is it the drug or is it the measure.

I think that, for the moment, we can't be certain except to know that both have failed. We can say it is the drug and, therefore, the measures couldn't have worked or we could say actually we thought the drug was pretty good, but the measures were not very good. It is sort of a cart and horse question.

[Slide.]

So there are a number of practical issues to consider when looking at these. The first is

what is the outcome that you are actually looking for and what is the fiber population that you are affecting.

So these nerve-conduction studies, as the neurologists know, are predominantly large-fiber measures. If you are looking for a drug that is going to affect a small-fiber function, then you wouldn't do nerve conductions because it is not going to get at it. But you might do either skin biopsies, which you will hear about, or quantitative sensory-testing measure to look at small-fiber function.

So this is an issue that comes up time and time again. Think about the fiber population that you want to affect, and then pick the endpoint measure that you are interested in. What parameter is going to get better? Is it a velocity parameter which happens very quickly if you improve diabetic control or is it an amplitude measure which is going to be most likely to take a long period of time and have a slower change because it is fundamental property of nerve regrowth and collateral reinnervation?

Last, as you can see, you fast will the intervention work? If you improve glycemic

control, nerve-conduction will change very quickly but then, after that, it is going to stay very stable while amplitude won't change except very late in the study.

That comes into the second issue here which is what, really, will your drug do? What is it going to affect? Is it going to affect velocity? Is it going to affect large fiber, small fiber, autonomic function and then you need to go into the top issue to pick the outcome choice that you want.

I think the last question comes up quite frequently. The answer is an unequivocal yes. All of these techniques can be done. With training, you can get away from this issue of the test is too complicated or the measure is so complex and there is such variability that nobody could ever do it and we have got to do something stupidly simple. The answer is it has been done time and time again.

You can do nerve conductions. You can do quantitative sensory testing in multiple sites. You just need a little bit of training like you do for a neurologic exam. I said here in the note that there have been some multicenter Japanese work that has been done looking at nerve conduction and

they have shown that F-wave is an extremely robust measure and probably, in their hands, the best measure in terms of reliability.

But, again, before accepting that, you need to decide, is the F-wave going to change in your trial and is that what you are interested in.

[Slide.]

Let me try and summarize because I think we ought to leave more of the time for discussion, clearly nerve conductions are the best studies and the most accepted tests. They correlate with measures. A change in time is real and that they can look at both worsening and improvement.

The other electrophysiologic tests are there. They are good, but a lot of them we need more data. That is what this NIH report to Congress is going to say in some respect. We have got to figure out can these others be done and can they be done in large populations over time.

That the nerve conductions are particularly important in my view as we think about disease-modifying agents, and, again, we will hear more of this from Eva, I hope, in these composite measures. The Peter Dyke one is the NIS(LL)+7. We have done TNS and Eva has done her own. But they

are all useful because they look at a variety of domains.

You can then begin to look the subdomains essentially suggesting a little bit of what Mark said, that there may be subpopulations or submeasures of these larger domains that improve at a time when the main domain may, in fact, not improve.

[Slide.]

I have not really talked about the issue as regards to symptom of neuropathic pain because I view that as symptomatic treatment. The electrophysiologic tests shouldn't be forgotten, either nerve conductions or quantitative sensory testing. Both we and Joe Arezzo and others have shown that these are extremely valuable in toxicity monitoring.

So, if you think your drug is going to cause a problem, even though it may help symptoms, these are very reliable measures to look at but they really don't have a use in outcome criteria for these kinds of pain studies because they look at large fibers which are not going to be affected and they are fundamentally not altering the disease.

Thank you.

DR. KATZ: Thank you, Dr. Cornblath.

Any questions from around the table for Dr. Cornblath?

DR. BRIL: I have a question.

DR. KATZ: Yes. Dr. Bril?

DR. BRIL: Thank you for that reminder of the importance of nerve-conduction studies. I guess my question had to do with the magnitude of change which is the essential question because the thing that we all see changing is conduction velocities.

One of the problems with using nerve conductions as a surrogate is what does it mean. So I would challenge you to just tell us and share with us the magnitude of change after transplantation, the magnitude of change in velocity or amplitude after a year or two after transplantation or after the insertion of an insulin pump because, although Peter Dyke has developed those quantitative measures that say you have to have 2 meters per second in order to detect a clinical change, I would be surprised if you can obtain that degree of change very easily in a chronic disorder such as diabetic neuropathy.

So could you just clarify that?

DR. CORNBLATH: Yes. The data, and this is one of these unfortunate things, that the kind of comparative data that you would like, Navarro has the best data from Minnesota on the degree of change in nerve conduction but they are not doing it in extent with NIS scores or NIS(LL) scores so it is a little bit of apples and oranges.

But these kinds of values are very easy to see after the several meter per second, after implantation of pumps or the beginning of insulin therapy. It is very common to see multimeter changes in their hands.

Now, they didn't go back and look at the change in terms of NIS(LL) or in terms of other quantitative measures.

DR. BRIL: But I think if you follow them out for five years, it may be a meter per second but it is not that quickly, that rapidly. The magnitude isn't that great in a short time after transplant.

DR. CORNBLATH: It can be when the diabetic control goes to normal.

DR. BRIL: Well, perhaps, in a few. But, over the long term, I think the mean changes are

not that great. If you see the non-transplant versus the transplant, they do separate, but slowly. The magnitude is not that great in mean numbers. Yes, in selected patients, you may have large shifts but you do that in almost any study.

DR. KATZ: Other questions for Dr. Cornblath? Go ahead.

DR. DWORKIN: It sounded like you were suggesting that the NIS(LL)+7 has considerable reliability and validity but all the data are from the Mayo Clinic. Is that the case?

DR. CORNBLATH: Eva can speak to that.

DR. DWORKIN: So that will be--thanks.

DR. KATZ: I have a question if nobody else does about the NIS(LL)+7. My understanding from the literature is that when the folks at Mayo were trying to figure out what degree of change in this composite disability score is clinically meaningful, they decided to focus on what the minimum change was that a physician, a neurologist, could detect in that exam.

So the two-point change in the NIS was arrived at based on the conjecture that that was the minimum number of points a physician could detect and then that, somehow, got translated into

that must be what is the minimal change that is clinically meaningful for patients.

My question is what is the evidence, actually, that that two-point change in the NIS is clinically meaningful for patients.

DR. CORNBLATH: Go ahead. This is a tag team.

DR. FELDMAN: Actually, the history of that is that the Peripheral Nerve Society met. Dr. Dyke chaired the meeting and there were probably about 100 of us there. A consensus was reached that two points was a meaningful change in the NIS. So that was done somewhat prospectively by a group.

I am fairly sure you are referring to Dr. Dyke's paper in Neurology, I think 1997 or 1998, where he, then, looks at the NIS(LL)+7, and I will be discussing this when I speak, and looks at the change in the NIS(LL)+7 over time, which David mentioned, and then, separately in that paper, says, but if we wanted to look at two points in the NIS, which is very different than the NIS(LL), and I will also explain that to you, then this is what we would supposedly need to see in terms of numbers of patients and time.

So that was very arbitrarily chosen.

There are data from Peter Dyke, though, looking, for example, at sural-nerve biopsies and comparing them to nerve-conduction velocities and degree of clinical impairment, as there are from other individuals, and I will also discuss that.

But this two points on the NIS was kind of grabbed from the sky.

DR. KATZ: So, if I am hearing you correctly, there really is no evidence that that is, in fact, the change that is meaningful to patients?

DR. FELDMAN: What I will do is show you composite scores where the NIS is a part of the composite score but whether or not--the NIS, itself, is a total neurologic exam so two points--I mean, you could have a cranial-nerve abnormality and that could give you two points. Or you could have shoulder weakness.

So it may not necessarily be relevant, the entire NIS. Now, the NIS(LL), which I will show you, is more targeted but still has a large motor component to it.

DR. CORNBLATH: If I could comment. I think you are absolutely right. I said "a clinically meaningful." I didn't use the words,

and you have added them, "to patients." So there is a thing that will come around which is can we take that and put it with some symptom score or some giant quality-of-life event. As far as I know, that has not been done.

Do you know that, that is a change in the NIS at the same time in a study looking at the NIS change with a QOL measure? I don't know that that has been done.

DR. FELDMAN: I don't think so, either.

DR. CORNBLATH: No; I don't think any of us know of that.

DR. KATZ: Dr. Shafer, I think you were actually on deck first. Did you still have a question?

DR. SHAFER: That was it.

DR. KATZ: Dr. Woolf and then Dr. Bril.

DR. WOOLF: You highlighted the difficulty, or the impossibility, with electrophysiology of looking at small-fiber function. I just wanted your views, the difference in susceptibility in terms of large-fiber between sensory and motor and you didn't mention sympathetic small fibers at all.

DR. CORNBLATH: As you know, the

techniques that are required are highly specialized and very difficult in terms of patient cooperation. As far as I know, they have not been used in trial, unless I am mistaken. So that is why I didn't bring them up. But, theoretically, one could look at these at C-fiber conduction, C-fiber spontaneous firing, but they are technically very demanding.

Is that correct? Yes? Thanks.

DR. KATZ: Dr. Bril?

DR. BRIL: I guess I had a couple of comments as well. I know we will hear more about the NIS. I think it is limited for diabetic neuropathy for various reasons which I am sure Eva will discuss when she is discussing the scales, partly because it is so heavily weighted to motor function.

But I guess I would ask Dr. Cornblath what he thinks. That scale just takes a couple of nerve-conduction parameters that seem to fit with the group. Should we just be doing one nerve-conduction parameter or do you think that if we are going to do nerve conductions we should do a full assessment? Should we do summary scales of nerve conductions?

How should we handle this large volume of

data and look at it, not combining it with clinical scales, but just by itself as a large-fiber measure, as the most accurate large-fiber measure we have. How should we actually handle it?

DR. CORNBLATH: Again, I think the issue is really what you are looking for if you are doing a trial in terms of drug development; that is, do you expect that your measure is going to improve conduction velocity, as you might in a demyelating neuropathy and as has been shown in CIDP for example, or do you think you are going to affect nerve function, itself, with connections at the end in either motor or sensory fibers over a longer period of time in which you would prefer to do amplitudes.

So I think, in my view, it is what you want to ask. You are going to get, as you point out correctly, a large number of measures and most of the either composite measures or, when it is done singly, have only selected out one or two of these.

Since you and I do these every day, there are ten or fifteen or twenty individual parameters that we get. I think what has happened is that the composite people, when we developed ours and when

Peter developed NIS(LL)+7, picked out those that either we thought were going to be helpful, so we picked out a motor and a sensory amplitude for TNS and he has picked out a number of other things for NIS(LL)+7.

But I think it ought to be prospectively thought based on what you think the effect is.

DR. KATZ: Actually, Dr. Farrar, you were first and we will keep going from there. Did you have a question, John?

DR. FARRAR: I really wanted to point out and would ask for your comment on the following which is that, ultimately, the real issue is what is the question. That is probably the first of many times that you will hear that over the course of the day.

I am not overly familiar with this particular scale, but the fact that there are motor components to it clearly is asking a different question than if there was a strict sensory neuropathy. You wouldn't be able to, perhaps, detect it with that.

I think the other issue I wanted to point out is that EMG and even quantitative sensory testing to a degree depend on a generalized

disease. Diabetes and postherpetic neuralgia are clearly very different. It would be very hard, I think, to find an EMG abnormality in someone with postherpetic neuralgia. I don't know whether that has been done.

I think it is important to keep in mind that this discussion is targeted at two very different issues, one of which is diabetic neuropathy and the other is nerve-induced pain. It is clearly reasonable to consider the two together because diabetic neuropathy is one of the causes of neuropathic pain.

But I would just like the committee and would ask your opinion about whether, in fact, EMG abnormalities or even quantitative sensory testing abnormalities are necessary for a patient to experience pain.

DR. CORNBLATH: That is why I broke that up in the summary. So most of what we are talking about in the use of neurophysiological electrodiagnostic tests is, absolutely you are correct, applicable to the so-called disease-modifying issue here. I don't think they play much of a role, if any role, in the other state. Mike probably has the best QST data in PHN

if you want to speak to that.

DR. BRIL: Could I just answer one thing to that. There are two areas, symptomatic improvement and then specific modifying disease. However, there are recent studies. There was a study I was involved in--I know it was retrospective but it showed that by selecting patients, depending on the electrophysiological severity, those who responded were those who still had residual nerve function that worked.

The role of electrophysiologic studies in a disease such as diabetic neuropathy in treating painful symptoms may be to stratify the patients and help determine or predict who would respond and that would be the role. I have seen that. There are some posters at the ADA that are going to say something similar.

So if you have sural response left, it predicts a response to the intervention as opposed to if you don't have a sural-nerve response left. So, clearly, the number of surviving large fibers really does have an indication to, perhaps, small-fiber function or response to pain. Now, not in postherpetic neuralgia or trigeminal neuralgia. Those are totally different disorders with

different endpoints.

DR. KATZ: Dr. Rowbothom, I think the specific question is what the role is for electrophysiology or quantitative sensory testing in clinical trials in postherpetic neuralgia, if you wanted to comment on that.

DR. ROWBOTHOM: Thanks. A few things. One is quantitative thermal sensory testing in postherpetic neuralgias can be readily performed. There are some difficulties in interpretation just because some patients have such a hyperalgesic response to heat stimuli and they fatigue very quickly. So it is difficult to do those studies.

What we have evolved towards is using that plus things like targeted application of capsaicin in the area of pain and evaluating the response to that and skin-biopsy assessments rather than relying on a single tool such as quantitative thermal sensory testing.

For most patients with postherpetic neuralgia, the great majority are going to have it on the trunk or on the face which are places that are just completely impossible to do conventional nerve-conduction studies.

DR. CORNBLATH: We wouldn't use then, in

any case.

DR. ROWBOTHOM: Exactly.

DR. KATZ: A specific comment about that issue? Dr. Dworkin.

DR. DWORKIN: When you are talking about QST and PHN, you are referring to it as a way of selecting patients and, perhaps, predicting treatment response or do you also mean with respect to an evaluation of treatment response as an outcome measure?

DR. ROWBOTHOM: None of our studies have actually used QST as an outcome measure over time. We did some work with looking at acute changes in it but not exactly what you are referring to that would be more analogous to the diabetic-neuropathy trials.

DR. KATZ: Dr. Rendell?

DR. RENDELL: With respect to Vera Bril's comments, it does raise an important issue because, in our diabetic-neuropathy trials, clearly David and Peter make a big issue of how well nerve-conduction tests are done. Yet, in pain trials, nerve-conduction tests are not done very well. They are not standardized in many trials and the question is should we be applying the same

rigor to nerve-conduction trials and pain trials that we are doing in functional trials of diabetic neuropathy.

DR. KATZ: Dr. Bril?

DR. BRIL: Absolutely. The trial that I spoke about initially was a symptomatic trial and the nerve conductions in that trial were done with the same rigor as some of the more specific trials. It was a post hoc analysis so it is weak, and who knows, and development has not proceeded with that particular agent.

But, looking at them, there was a clear separation with and without surals. Then there is more recent work that is being present at the ADA that showed changes in a composite symptom score or positive symptoms of neuropathy and those determined somewhat by the presence or absence of surals.

So I would say yes, definitely. In the studies of diabetic neuropathy. Now, I know this isn't very popular in a lot of pain clinics because a lot of patients have advanced disease and lack surals and there is always the wish to include these patients in trials as well, and so maybe they should be, but a stratification done with respect

to who has surals and who doesn't, and since surals can be technically challenging, yes; they have to be done with the same rigor.

DR. KATZ: Dr. Shafer?

DR. SHAFER: Bucking the trend, I am going to direct this question to the speaker.

DR. CORNBLATH: He prefers not, but--

DR. SHAFER: What I have heard is that these tests on nerve conduction with proper training and guidance can be objective and reproducible, although that is obviously a source of some debate here. Also a source of some debate, but, in your opinion, is that they can show changes in a tractable time course for a clinical trial.

If that is the case, if a company wished to make a claim that preservation of large-nerve function was a good thing and that they had a drug that would help to preserve large-nerve function in diabetic patients, would neuropathic-pain studies be appropriate as a primary endpoint for a clinical trial?

DR. CORNBLATH: I think they would because, as we heard before, you could say it is the proper question driving the choice of the endpoint. If the endpoint, you believe, is that

you can save sensory-nerve function and one measure of doing that is to look at the amplitude of the sural response done by trained people in the same way where, again, I really do believe that the issues of reliability, variability, et cetera, inter- and intra-rater reliability are all put to rest, then you are asking the right question.

You are asking for the right measure. But all you need now is some knowledge of the magnitude of change over time in that measure in the target population. That is, I am sure Eva will say, one of the things that we are missing because that kind of information is either out there for the Rochester study or hidden proprietarily in many of the companies who have done negative studies.

Some of it is published but a lot of it is hidden within centers. But I think you could ask that question and it would be appropriate. We have to get to the issues that the Chair raised about what is meaningful. Is it okay to have your amplitude be 1 microvolt better than the other group?

DR. KATZ: I am going to take the prerogative of calling for a break now. These are all questions that will fill the rest of our day's

discussion and I am sure we won't lack them. So let's resume in fifteen minutes.

[Break.]

DR. KATZ: Dr. Eva Feldman now will speak to us on scales used for the evaluation of peripheral neuropathy. Dr. Feldman?

Scales Used in the Evaluation of Peripheral Neuropathy

DR. FELDMAN: Thank you very much. I am really very pleased to be here today.

What I think I am going to do is maybe take one step back and define diabetic neuropathy as we see it as neurologists and I believe as probably most clinicians see it and then tell you about scales and really an historical manner and how they developed over time, and really highlight some of the major trials that have already occurred that have, unfortunately, not been successful as we have heard, and then end by trying to pull together what I think are the best composite scales that are currently available.

[Slide.]

So, as you can see here, the definition of diabetic neuropathy--it has been defined by the World Health Organization as a disease

characterized as a progressive loss of nerve fibers eventually leading to sensation loss, foot ulceration and amputation.

[Slide.]

Here is, I will say, is the star of the hour and that is the myelinated nerve. I just really wanted to remind you, the nerve cell body that we are interested in lies either in the dorsal-root ganglion neuron for the sensory nerve or the spinal cord for the motor nerve. It gives out this large axon that has to transverse down the length of the arm or the leg.

Then there are these nerve terminals. In a sensory nerve, as you know, these nerve terminals then bring afferent input into the spinal cord and, in a motor nerve, there is efferent output that goes out.

Now, the terminology in the peripheral nervous system is actually a little confusing. Many people refer to this as a nerve.

[Slide.]

But, as you can see in the next slide, this nerve really lies in what is also known as a large nerve fiber or a nerve bundle. So there are multiple individual nerves in these individual

fascicles and theses individual fascicles of nerves together make up either a pure sensory nerve, a pure motor nerve or, more commonly, a mixed nerve.

What is important is I have shown you an example of the myelinated nerve but, as you have heard earlier, it is not just myelinated nerves that we are interested in but in this mixed nerve bundle, in this fascia, there are also unmyelinated nerves and thinly myelinated nerves. These nerve fibers carry distinct types of information.

[Slide.]

In the peripheral nervous system, damage due to diabetes is thought to primarily be axonal in nature, at least initially, although there likely is some demyelinating component, some attack in the myelin in the peripheral nervous system.

Here is just an example, a diagram, showing distal axonal loss of a neuron. We also believe that there could be primary insults to the dorsal-root ganglion neuron. But what one then sees, though, is distal loss of nerve function really mimicking, then, the pathology. Again, depending on what nerve fiber type is involved, that would, of course, then, depend on what type of symptoms and signs you would find as the clinician.

[Slide.]

So neuropathic systems and signs, to summarize, are going to reflect the type of nerve-fiber damage. I think, very importantly, and it has been alluded to today, but diabetic peripheral neuropathy is primarily a sensory neuropathy. These thinly myelinated or unmyelinated fibers that we have been discussing, they mediate pain, alter cold, heat and light touch.

These are the fibers that are difficult to measure on standard nerve-conduction studies and really require more sophisticated techniques that are not routinely done in clinical trials. In contrast, the large myelinated fibers, these carry vibration, proprioception, your position sense from the mechanoreceptors. These are easily measured on nerve-conduction studies.

Most frequently likely both fiber types are involved in diabetic neuropathy but it is very important to understand that the pain component of neuropathy is more likely mediated by the small-fiber component although there are people who believe that joint pain is a component of neuropathic pain and we could discuss that this

afternoon.

So it isn't just one simple disease. There are some patients who have very painful neuropathy and when you examine them, they have normal nerve conductions, normal vibration and normal proprioception. Then there are some patients who have little pain and when you examine them, what you see is sometimes light touch is moderately intact but they have a large loss of vibration and proprioception.

So this disease can selectively affect different fiber populations although most commonly it does affect both, although we don't understand why some people have more pain than others and we will discuss that later also.

[Slide.]

To now put things in context, you can imagine a patient that has selective disease of, say, a group of large myelinated fibers and small myelinated fibers in a distal to proximal gradient. That will then cause the symptoms that the patient most notes.

[Slide.]

These symptoms can be acute in onset or very insidious. The course of the symptoms that

patients complain of could be monophasic, meaning they start and they just kind of keep on going, or they can be fluctuating with or without drug intervention sometimes dependent, of course, on glycemic control.

Now, the sensory symptoms; really, as a neurologist, we talk of two types of sensory symptoms. You can have what we call negative symptoms. That is the patient is numb, and they really have loss of sensation. They are not going to come to you as the clinician and say, I'll come to you to enter a trial in pain, because they really have just what is called the insensate or numb foot. That is believed to account for about 80 percent of the patient population that has diabetic neuropathy at any one time.

In contrast, those patients who have tingling, prickling, burning pain, those are called positive symptoms. Those are believed to account for approximately 20 percent of the patients at any one time.

Importantly, and this will be very important when we talk about the scales, you know, real motor symptoms are rare in diabetic neuropathy. Certainly, there is a subset of

patients that have motor involvement, but this is primarily a sensory neuropathy and we need to keep that in mind as we are looking at scales.

[Slide.]

Now, the signs that you see when you examine a patient and this becomes, again, important as we design our clinical tools for our trials, is you will see a dry, atrophic skin in the feet, loss of hair and sweating and, in more advanced cases, distal muscle atrophy. Sensory, again, findings are the most common and we have already talked about the large-fiber findings, the vibration and proprioception and then the small-fiber findings of light touch and pin prick.

Motor would be distal muscle weakness. Let me emphasize distal because when I talk about the NIS(LL), that has a large component of proximal motor examination which then makes it not really relevant to us. And then reflexes are either absent or depressed.

[Slide.]

So, in summary, anatomic changes that I have discussed, leads to these signs and symptoms giving you this class of diabetic peripheral neuropathy, this stocking-glove pattern that

everyone discusses and that we have all seen as clinicians.

[Slide.]

Up until I would say approximately the mid-1980s, the diagnosis of neuropathy and the epidemiological studies were really somewhat--oh, they weren't particularly prospective. They were mainly retrospective. There were some prospective trials but they were done as the clinician so decided to do it, like Peral looked at 4,400 patients and he used vibration as the way to determine whether or not they had neuropathy.

It wasn't until the San Antonio consensus statement occurred in 1988, and this was formed by a consensus statement from the American Diabetes Association and the neurologic community led, in part, by Peter Dyke and also Jack Griffin from Johns Hopkins, that it was said that if you are going to look at diabetic neuropathy in a quantitative fashion for a clinical trial, you should look at some sort of clinical scale.

At that time, the Neurologic Disability Score, which is the mother of the NIS, or the father, considered the quantitative sensory testing, autonomic function testing and nerve

conductions. Based on abnormalities in these, patients were actually staged as Stage 1A through C if they had no symptoms, and these would be positive symptoms, or Stage 2A through C if they had positive symptoms.

One of reasons this all happened is that, at the same time historically, the DCCT was being designed and occurred. As you recall, in the DCCT, neuropathy was examined.

[Slide.]

The way the DCCT was designed, and remember, it is occurring in parallel with San Antonio consensus criteria, is they decided to define diabetic neuropathy by simply a clinical exam by a neurologist in nerve-conduction studies. The clinical exam was very simple. You looked at sensation, small and large fiber, and ankle reflexes. There was a symptom score. If two of the three were positive, meaning sensation, if you had abnormalities in sensation, reflexes or the symptom score, you had probable diabetic neuropathy.
If you had all three, then you had definite neuropathy. Nerve-conduction studies were also performed on the DCCT patients. This, I

think, was useful and could prove to be useful to us in the future on 1,243 patients at baseline and five years later. The perineal motor nerve conduction was 3.5 meters per second faster in the intensive versus the conventional treatment group after five years.

This is one of many studies that shows that the perineal nerve conduction, while it is a motor nerve and I have told you that this is primarily a sensory disorder, this particular motor nerve, as in some studies, the medium motor nerve, the conduction velocity does appear to be possibly a good surrogate marker for disease progression.

[Slide.]

Here is, actually, the neurologic outcome of the DCCT. I think this is interesting to see, if you want to look. The black are the intensive patients and the hatched the conventional. You can see the difference in terms of better outcome in the intensive group when it comes to nerve conductions in neurologic examination, and also autonomic-function studies were done. Our variability was done in the DCCT.

[Slide.]

I am going to show you this slide because

I would like to make a pitch. The DCCT patient population is currently being followed as the EDIC population, so they continued the DCCT, as you all know, for another ten years. The only part of the neurologic examination that is being done as something is a tool that we developed, that David mentioned, called the MNSI, the Michigan Neuropathy Screening Instrument.

It is a very simple tool. What it shows, and I am not going to go over it in any detail, but just it does show that if you look at the percent of patients with neuropathy by the MNSI, those people who were on intensive therapy remained with a lower percentage of neuropathy than those patients on conventional therapy in both the primary and the secondary cohort.

I show you this not to tout the scale that we developed but rather to say that these patients would be available for nerve-conduction studies and that would give us, over time, nerve-conduction studies in a well-classified patient population at Time 0, or say, Year 0, Year 5 and then later on. They are now entering approximately Year 9, maybe Year 10.

[Slide.]

About the early '90's--so the DCCT is ongoing. We don't have those results. We have had the San Antonio consensus criteria and now people begin to look at drugs in the treatment of diabetic neuropathy and, really, what primary endpoint to use, what should be the primary efficacy point.

This was a really hot topic of discussion as it continues to be. Let me show you the results of three trials, two of which are aldose-reductase inhibitors. The tolrestat was a drug, and aldose-reductase inhibitor, and was brought into clinical trial, a fairly well-designed large-scale placebo blind clinical trial.

Some of the trial design emanated from two previous ARIs, one known as sorbinil where nerve biopsies had been done before treatment, then after twelve months of treatment and then a second nerve biopsy was done. Actually, morphometry on the sural nerve biopsies were looked at in the sorbinil and a probable positive effect--well, actually, the sorbinil trial did not show a probable positive effect, did it? I am getting that one confused. That is so long ago.

DR. BRIL: The morphology was done in a single site. The morphology did show a positive

effect that was published.

DR. FELDMAN: That was right.

DR. BRIL: But the electrophysiology in the multicenter trial did not.

DR. FELDMAN: Did not. That's right. That's exactly right. There was a positive effect not confirmed by electrophysiology. That, however, led to the development of using actually paired sural-nerve biopsies as the primary efficacy point in clinical trials with diabetic neuropathy.

This was frequently paired with nerve-conduction studies. But, in the trials I am going to discuss, nerve-conduction studies were a secondary endpoint. So, in the tolrestat trial, the primary efficacy was nerve morphometry and sorbitol content, aldose-reductase inhibitors. What they do is they decrease the conversion of glucose to sorbitol. So if you use an ARI, you should measure less sorbitol in the nerve.

The secondary parameters were nerve-conduction velocities, a clinical exam and a clinical exam. After a twelve-month analysis, there appeared to be no effect on sural-nerve biopsy on the morphometry and I am going to show you some pictures.

However, there was, probably, a mild effect on motor-nerve-conduction velocity which was discussed but the study, itself, was terminated although, in a small subset of patients that continued to get the drug for a longer period of time and actually had a nerve biopsy at a later point, it appeared that potentially the drug was efficacious in those patients.

But that drug also had some mild toxicity. So a second aldose-reductase inhibitor, zopolrestat, was then brought to a Phase III clinical trial. Actually, Dr. Arezzo was very involved in this particular compound and might speak to it.

The endpoints with zopolrestat were similar to tolrestat in the Phase III clinical trial. So, again, they used nerve morphometry. Unfortunately, they used half the dose they used in the Phase II clinical trial which showed a very robust effect on nerve-conduction studies, and they did an 18-month interim analysis. They did elect to do this trial for three years and there was no effect on sural-nerve morphometry. So the trial was discontinued.

Alcar, which Vera mentioned earlier, an

excellent trial done by Hoffman LaRoche, used as a primary endpoint nerve morphometry and nerve-conduction studies and there was no effect.

So, at this point, there was some discussion in the neurologic world as well, I think, in the FDA whether actually doing bilateral paired sural-nerve biopsies on patients was a necessary primary endpoint.

[Slide.]

Here is an example of sural-nerve biopsies, and I will go back to that diagram I showed you earlier. Here is a cross section of a nerve and here, on high power, you see multiple large myelinated nerves and you see some small thinly myelinated nerves.

These patient samples are still available for study. They are under the care of the University of Michigan and we are glad to give those out with certain requests. There is a protocol that needs to go through with ourselves and the companies.

[Slide.]

What happened is then these individual nerve biopsies were then quantitated on the computer. The red boxes, for example, are large

myelinated fibers and the blue boxes are a different fiber class. So there was very elegant nerve morphometry done on these biopsies.

[Slide.]

Here is an example of a nerve histogram that was generated from one of the sural-nerve biopsies from the trial. You can see, in this particular fascicle, the definite axon loss compared to what I showed you before. And here is a typical myelinated fiber histogram that was generated. So it is important to know that this has been done.

In some ways, maybe the most sensitive measure, it showed no effect but was it the measure or was it more likely, as most people believe, the compound or the small time in which the compound was administered.

[Slide.]

Now let's go to another aldose-reductase inhibitor that I think will teach us even more and that is the aldose-reductase inhibitor Zenarestat. It really began, interest in it, after tolrestat had failed and zopolrestat was working. It was under clinical trial. Zenarestat occurred and the entry criteria for Zenarestat to enter this study

and this is important in relation to what Vera was saying is you needed to have two of three of either symptoms, signs, abnormal nerve conductions in two nerves or abnormal vibratory perception threshold, QST.

However, importantly, you had to have both surals present. They could be abnormal but they had to be present and your vibratory perception threshold had to be recordable. They did a Phase II 52-week trial, double-blind placebo-controlled, reported the results in Neurology. It was very promising.

I'm sorry; I should tell you also that, in these patients, they also did biopsies. But, along with the biopsies, they did quantitative sensory testing which was very good and they did a quantitative neurologic exam.

[Slide.]

Here are some of the results. If you look at the sural sensory-nerve-conduction velocity, and this is meters per second, they saw a dose response from their drug in the sensory-nerve-conduction velocity in change at baseline to final. They did a nerve-conduction composite which I will tell you a little bit more about but, again, they saw an

improvement in, if you looked at from placebo to their highest drug, baseline to final.

That correlated with nerve-fiber-density changes. So here are fibers per meter squared. Here they had a loss. A loss was seen in the placebo group but there was a dose-dependent response with actually a positive effect on fibers per meters squared by morphometry. So this was very exciting.

[Slide.]

These are the actual data from the paper. I think it is important to see--the change is here in the black. What is important to see about that is the changes are all in the very thinly myelinated or small myelinated fibers. Those would be in the small myelinated fibers, the pain and temperature fibers.

[Slide.]

So, from that, they decided to do a Phase III clinical trial and this was really somewhat of a breakthrough and to not propose to use morphometry but, rather, say, look, we have seen very good surrogate markers in terms of nerve-conduction studies and in terms of quantitative sensory testing so let's use that in

lieu of doing paired bilateral sural-nerve biopsies.

This is the first trial, to my knowledge, that also suggested to use a composite score. So what they suggested to use is a composite rank score for the median four-arm sensory, perineal, motor and sural sensory-conduction velocities, so three sensory-conduction velocities, plus they had a composite rank score of the QST, of quantitative sensory testing, for vibratory and cool perception.

You can see what their secondary endpoints were; nerve-conduction velocities, F-waves, amplitudes. This is the Michigan Diabetic Neuropathy score which I actually think has too much motor in it now. When we developed it six or seven years ago, I think we were more naive. A health-related quality of life.

Unfortunately, this study, where an interim analysis looked promising, was discontinued because the patients developed probable renal toxicity and increase in creatinine. It is unfortunate because this could have been a trial that could have given us the answer about true composite endpoints as a compositive score for a primary endpoint.

[Slide.]

The next and final trial that I am going to discuss is the nerve-growth-factor trial. Nerve growth factor was administered subcutaneously in the Phase II clinical trial to 250 patients. I want to make this point because it is so important as we talk about trial design, and that is nerve growth factor is certainly going to be efficacious in small fibers and you are going to be able to measure its efficacy by seeing changes in heat, cold, probably light touch.

You would not see its efficacy if you measured motor function, if you measured any large-fiber function, if you measured ankle reflexes. So, it is important. You are really looking here at a drug that should primarily have only a small-fiber function.

Here are some of the details of the study. The Phase II clinical study was given subcutaneously and small improvements were seen in sensory symptoms and QST. Unfortunately, this is the neuropathy-impairment score. To show you maybe a little bit of my naivete, I thought there were just going to be a few of us around the table so I brought five copies of this.

So I am going to just tell you because we are going to talk about the NIS in a few minutes. But what it is, and I am sure you can't see it, is this part is a cranial-nerve exam. These are all measures of muscle strength. These are reflexes. This is measure of sensation in the hand. Just these last four measures are sensation in the foot.

That is the entire NIS. Let me just tell you for a slide in a couple of minutes, five minute from now or three minutes from now, that NIS(LL) that David was referring to, that has kind of somewhat become much the standard right now. What it is is 17 through 24 here on the NIS. That is looking at hip flexion. That is looking at knee extension, ankle dorsiflexion, plantar flexion, so it is a lot of proximal muscle strength. That is important to know.

The NIS(LL) looks at the knee reflex and the ankle jerk and then it does the large- and small-fiber function in the foot.

[Slide.]

But the NIS was used in the NGF trial. What they found was a change in the lower-limb NIS with NGF and it appeared to be dose-dependent change looking at the placebo. However, we now

believe, because of the Phase III clinical trial--this is because these patients were unblinded--when you got the NGF, it stung. When you got the placebo, it didn't.

It is generally held by both the people who devised the trial as well as the principal investigator that that is likely what happened.

[Slide.]

There were potentially changes in cold-detection threshold and heat-perception threshold in the NGF study although they were not necessarily as dose-related. But there was a definite difference when compared to the placebo. Now, importantly when you do quantitative sensory testing, you know the patient has to be able to cooperate with you. It is unlike nerve conductions where they can just lay there and you do it to them.

With QST, they have to be able to cooperate. So there was also a question of unblinding.

[Slide.]

The Phase III clinical trial, 1,119 patients. The primary was a change in the NIS(LL). So I have just told you that that is probably not

the best measure to choose because this is a small-fiber--NGF would be a small-fiber function and, on the NISLL, there are only two points that are looking at light touch and pain with a pin that potentially have changed. You see the secondary endpoints were the QST, a symptom and change questionnaire which I also brought, if anyone is interested in seeing, nerve-conduction studies which shouldn't have changed and also using a monofilament which possible could have changed because that is light touch. That was an unsuccessful trial.

So what have we learned from all of this and where, really, do we stand?

[Slide.]

Here are the measures that are currently in clinical trials because I think, as you well know, we are currently doing clinical trials and also these are measures that are being proposed to use in clinical trials. I should say that these are clinical trials looking at the drug that really going to affect the pathogenesis of diabetic neuropathy. This is not talking about, obviously, a drug for pain.

The current test is the NIS(LL)+7. What

is the +7? It is vibratory-perception threshold. It is RR variability with deep breathing, so it is actually a measure of autonomic function and five nerve conductions; perineal--that is the motor nerve in the leg, looking at its size, its conduction velocity and its distal latency; the tibial nerve, another nerve in the leg, looking at its distal latency; and then the sural, which is the sensory nerve in the leg, looking actually at its amplitude.

Importantly, what this +7 means is if you have an abnormality in one of those tests and it is between the 95th and the 99th percentile abnormal, you get one point. If you are greater than 99, you get two points. Then what happens is you really get an added composite score.

As David told us so nicely, in the Rochester diabetic cohort, there was, in one year, a change of 0.35 in those patients that they believe do not have diabetic neuropathy while, in those patients who do have neuropathy in this composite score yearly, they saw a change of 0.85.

They also published a very nice paper that shows that this NIS(LL)+7 correlates with other microvascular complications, particularly--well,

obviously, the two others, retinopathy and nephropathy. So it is a composite score looking at motor-nerve-conduction function, autonomic function, motor strength, reflexes and sensory examination in the lower extremity.

Here are some of the salient references.

[Slide.]

I think that, importantly, as I have pointed out, the NIS(LL) is primarily a motor test and when you actually go into Dr. Dyke's excellent papers, he says the same thing, that when you look at the NIS(LL) and see what is actually abnormal in patients with diabetic neuropathy, what you find is that reflexes and vibratory sensation are what is abnormal and there are essentially no motor abnormalities on the NIS(LL).

So you can imagine, because of the multiple points it has, if you are just primarily looking at sensory, how you can get a confounding effect in a clinical trial because in inter- and intraobserver variability and testing so many points that really are not relevant for your disorder.

This idea that reflexes and vibration sensation are most frequently abnormal has been

corroborated by a large study by Fedele and colleagues in 2,300 patients. What Dr. Dyke also has reported from the Rochester Diabetic cohort is the motor-nerve conductions of the lower extremity, the perineal nerve and the sural snap, are the most frequent abnormal nerve conduction.

So if you are just going to do two, you would do the perineal and the sural. Fedele also showed that. Dr. Dyke has also shown, in the Rochester Diabetic cohort, that vibration perception threshold is easier to measure, more reliable, and usually more often abnormal than cold-perception threshold.

I believe that is a question whether RR variability is a viable clinical endpoint. It seems like, if you are really--you know, in some ways, if you are primarily looking at somatic sensory-motor peripheral neuropathy, I am not sure you want to confound your measurement by looking at the RR interval, which the NIS(LL)+7 does.

[Slide.]

So I decided I would propose a clinical composite score. This is, again, the--these are the last two slides of my talk. What I would like to propose based on, really, having done many of

these studies and, primarily, though having reviewed the literature is a NIS(LL) but minus Questions 17 through 22 or maybe 14 through 24. That is really getting rid of testing hip strength and quadriceps strength, all this proximal strength, so that the clinical exam, really, then becomes focused on what one sees in the disease and that sensory loss in the lower extremities, ankle-reflex loss.

Potentially, we could look at very distal weakness. If we did, we would keep in Questions 23 and 24. That is toe extensor and flexor. I believe a composite nerve-conduction-velocity score is a good idea. I think the perineal motor nerve appears to be the one that has been used the most, most reliable in multiple trials, and also the sural-nerve amplitude, although there is more variability in measuring that, as David and Vera and Dr. Arezzo also will tell us, that also appears to be a reliable measure.

Quantitative sensory testing? BPT is more reliable and reproducible than CPT but we also need both because we need a measure of large and small fibers. Secondary endpoints, I think, should be a symptom questionnaire, maybe a quality-of-life.

[Slide.]

I think that I would like to summarize by saying that our experience over the last twelve years, in my mind, clearly shows that drug efficacy in DPN and diabetic polyneuropathy cannot be judged by just one single parameter. It is just really too complicated a disorder, as I have tried to portray for you today. I believe what we need to do is develop a good composite score.

I am happy to take any questions.

DR. KATZ: Thank you very much, Dr. Feldman.

Dr. Dworkin, you are first.

DR. DWORKIN: It seems to me that treatment responsiveness is one aspect of establishing validity.

DR. FELDMAN: Right.

DR. DWORKIN: But to go back to your original definition of diabetic neuropathy, you emphasized foot ulceration and amputation.

DR. FELDMAN: Right.

DR. DWORKIN: So my question is do any of the measures that we have heard discussed this morning in prospective studies establish themselves as risk factors for either foot ulceration or

amputation, which I might want to propose is the gold standard for a validity of one of these surrogate endpoints.

DR. FELDMAN: There is some very nice work from Andrew Bolton in England who has looked at vibratory-perception threshold over time and then the development of foot ulceration. He has shown a correlation between decreased vibratory-threshold sensation, VPT, over--this was a very long study--until, essentially, VPT is absent. And then the patients develop foot ulceration.

As you probably know, a diabetic has about a 15 percent chance in his or her lifetime to develop foot ulceration. So the problem, of course, with using foot ulceration as an outcome is that we are talking ten, twenty, twenty-five years into the disease. That is really end stage.

I do think that a feeling that we all have in this area is what we want to do, and I threw this on as it would be nice to treat patients early in their disease. So I really do think that we do need entry criteria which I didn't think I have time to talk about.

But, in my mind, our aim ought to be to halt progression. I am less likely to think we are

actually going to show improvement. I know that is not necessarily a popular view to take, but I think, hopefully, if we could just halt the progression of what is really kind of a relentless progressive neurodegenerative disease.

What I would propose is we enter patients who are very early in their disease but using a fairly protracted time course. I would say we probably need at least a three-year study.

DR. KATZ: Dr. Bril next please.

DR. BRIL: Andrew has also extended that work using some electrophysiology to look at prediction of foot ulceration. So these surrogates are now being tied more and more strongly to long-term neuropathy outcomes.

DR. KATZ: Dr. Farrar, did you have a question?

DR. FARRAR: Since clinical trials are so dependent on selecting the right population, I wonder if you could comment on your sense about whether the criteria used to decide whether or not people had sensory-reflex or symptom scores where appropriate and how, actually, that was decided.

DR. FELDMAN: So this would be in the Zenarestat trial or any trial--whichever trial I

would like to talk about?

DR. FARRAR: Are they different?

DR. FELDMAN: Oh; they are different. They are very different. Currently, there is a drug, alphalipoic acid, where patients can have actually a relatively neuropathy, no obtainable sural responses and very poor vibration-perception threshold and be entered into the trial.

I think that most trial, however, and, again, I want to defer to my colleagues if they would like to add anything, most trials have tried to use patients who have what we would say mild neuropathy, maybe at the extreme moderate, so that sural amplitudes needed to be present and they needed to be measurable reproducibly.

But if the surals were normal, then you needed to have another abnormal measure to go with it. So patients who had mild abnormalities in their sural nerves and a mild decrease quantitatively in vibration-perception threshold or cold-perception threshold, in my mind, would be the ideal patients to enter.

So the idea is that you if have got nerves of wood, if all the nerves are dead, there is not going to be a Lazarus effect which is what was

discussed in the mid-'80's with the ARIs. So I think we need to see early patients because the disease is going to progress. If you want to halt the progression, you have got to be able to monitor the progression. So you have got to be able to see the surals go down, the perineals get slower, the vibration-perception threshold change.

DR. FARRAR: Let me just follow up with a quick question.

DR. FELDMAN: Yes; please.

DR. FARRAR: Very specifically, how did they decide if the reflexes were less or not? As a neurologist, I have trouble doing that in most of my patients.

DR. FELDMAN: So reflexes were graded. In the NIS, and in most of these scores, the reflexes are graded simply as present, present with a gendracic maneuver or absent. So it is a very straightforward thing.

DR. CORNBLATH: That's not right.

DR. FELDMAN: What; in the NIS. The most recent NIS? OC?

DR. CORNBLATH: No; the NIS was always normal, reduced or absent.

DR. FELDMAN: Oh; I'm sorry. The NIS was

normal, reduced or absent.

DR. CORNBLATH: So that was a choice and that was determined that those three that neurologists could rely upon determine--

DR. FELDMAN: Thank you, David. That's right.

DR. CORNBLATH: The gendracic has nothing to do with it.

DR. FELDMAN: That was in the Zenarestat study, I'm sorry, that they used that. But one thing that Peter Dyke did evolve over time, which I think is important, is that NDS, the Neurologic Disability Score, that had, for example, in sensation, I think five choices and, in reflexes, four or five choices. What he did is he simplified things.

When he did do that, then, within the Mayo Clinic, several individual physicians would examine the same patient and he found a great deal less variability between examinations when he simplified his scores. And we would all agree, of course.

DR. KATZ: Dr. Cornblath.

DR. CORNBLATH: At the risk of touting my own horn, Eva, we have developed a scale, as you know. It is called the Total Neuropathy Scale. I

think one of the things Cynthia and I were talking about in between was what are some of the difficulties with the NIS.

DR. FELDMAN: Right.

DR. CORNBLATH: I think one that you alluded to but didn't directly mention is this very important issue that these are length-dependent neuropathies. As a result, if you have neuropathy up to your ankle, the likelihood, as you suggested, of showing a drug that will change sensory function at the great toe, which is what the NIS looks at, is highly unlikely. It would be, as you said, a Lazarus effect.

So what we did, in designing ours, was to us this opportunity of length-dependent to essentially assign points from a 0 to 4 scale depending on the length. So one of the very serious criticisms of NIS is this dependence upon the great toe and subsequently, then, the opportunity to change function at the great toe which you and I think is highly unlikely during the course of a clinical trial.

That includes changing the vibratory threshold or cooling threshold which is also measured at the great toe during a trial. So what

we did in TNS, as you know, is to change the great toe to a length issue saying it is either bad up to knee, up to the ankle, to the toe or normal. So this is another method to get away from one of the many criticisms of NIS.

So there are other composite measures around. You have a composite measure.

DR. FELDMAN: Yes; I did not talk about mine, either.

DR. CORNBLATH: I think that one of the issues for discussion is are we going to be left, at the end of the day, fooling with the NIS and trying to alter it to fit what we want or, in fact, does the NIS have such severe limitations that, in fact, it can't be used in this disease, again because of the biology of our understanding of what is possible.

DR. FELDMAN: Those are excellent points, David, and I apologize, really, for not discussing your scale or my scale or other scales. The scales I chose to discuss were those that are currently in clinical trial for diabetic neuropathy. And Vera has a scale also. So we all have scales.

The thing that is common about our scales--the scale team--is that motor strength is

deemphasized and it is emphasized in the NIS. I have now pounded this to death but, also, as David so nicely pointed out, these scales also look at a length-dependent sensory loss which I think is very important.

David's composite score also has a component of--you also have nerve conductions in it.

DR. CORNBLATH: We have nerve conductions, a simple vibratory threshold. We have large- and small-fiber function and we don't have yet, but we could easily take out one of those and put in something else for, again, a specific biological indication.

DR. FELDMAN: So it is a good composite. I think your score is a very good composite score. You have used it in a trial of suramin toxicity, haven't you?

DR. CORNBLATH: So far we have used it in monitoring in three chemotherapy things for toxicity. We have not had the opportunity to use in longitudinally.

DR. FELDMAN: The idea, though, that I think you are hearing is that prospectively, when a pharma comes to you, what we would suggest is a

composite trial that emphasizes sensory loss, that has a quantitative component and has a motor-nerve-conduction component.

DR. KATZ: Dr. Rendell, you were next, if you still have a question. Oh; sorry. Dr. Shafer?

DR. SHAFER: You mentioned, in passing, the work done by DCCT. I happen to have the DCCT database in front of me. They did a ton of testing and it appears that they actually did it yearly, but perhaps it was not done as frequently as yearly, on sural, perineal, median nerve, both motor and sensory amplitudes and conduction velocities.

Of course, it is such a huge study and so well controlled, would there be any point in going back to that database and trying to ask whether or not one can develop yet another scale from it?

DR. FELDMAN: I brought, actually the nice person who let me in the room--I actually brought a suitcase full of papers in case. Again, I thought there were going to be five of us sitting around a table. So I have all the DCCT papers and there was a paper done by the DCCT working group published in Neurology in 2000 where they looked at all the nerve conductions in detail and made associations,

et cetera.

I have got that paper there. What I think would be more useful would be for us to restudy those people now. We would actually have a really good well-defined population and really understand over a ten-year period what happens to nerve conduction in a group that is still relatively well-controlled that is interesting and a group that is less well-controlled. That is really the way EDIC has fallen out. But I will give you those papers.

DR. KATZ: Dr. Woolf, you were actually next.

DR. FELDMAN: But not much was out of it, though, except for perineal motor-nerve conduction, I should say.

DR. WOOLF: A key concern for us all here is why do trials fail. We have heard either the drug or the outcome measure. I think the nerve growth-factor trial is a classic in that case because the outcome measures did not measure the time to--conduction velocity does not measure C-fibers.

The testing, with the greatest respect--light touch is not a small-fiber test. It

is an a-fiber. It may not be the large proprioceptors, but they are large myelinated fibers and they are not NGF-responsive.

DR. FELDMAN: No; I stand corrected.

DR. WOOLF: The morphometry, again, is large fiber. You need electron microscopy.

DR. FELDMAN: Right.

DR. WOOLF: So, by all those three standards, the composites exclude the very fibers that are being targeted by the drug and so that trial will fail before you even start it.

DR. FELDMAN: Well, it did fail, as you know.

DR. WOOLF: I know. But you could predict it.

DR. FELDMAN: I know. And it was predicted by many. As many of the neurologists in this room know, it was predicted to fail. So that was a frustrating point. But you are right.

DR. WOOLF: So you have made a very convincing case how the composite studies were geared towards motor weakness which is no longer relevant. I would say that any composite measure has to include small-fiber measures, however difficult they are, because, otherwise, you are

going to have the same problem.

DR. FELDMAN: Would you be happy with cold-perception threshold, then, from quantitative sensory testing which appears to be--you know, in these large-scale clinical trials when we want to enter 1000 patients, that is probably truly doable and relatively reproducible. I think some of the more sophisticated electrophysiology probably really isn't doable.

DR. WOOLF: It is certainly better than nothing but I would like at least one other objective measure.

DR. KATZ: Dr. Woolf, just pursuing that further, do you have a specific thought about what would be the best objective measure for small-fiber function in such clinical trials?

DR. WOOLF: Function is very difficult, I accept. But morphometry, you can do electron microscopy. You can, actually, count the number of unmyelinated fibers and there are now unmyelinated fiber markers as well.

DR. FELDMAN: I think that the neurologic community really came out somewhat in force and I think backed by our endocrinology colleagues, kind of together, that probably bilateral sural-nerve

biopsies were not necessary in this disorder and too invasive

Also out in my suitcase of papers are two papers looking at the outcome of patients with bilateral sural-nerve biopsies comparing diabetic with nondiabetic patients. There does appear to be more likely to have persistent pain. So there is a morbidity to a sural-nerve biopsy in a diabetic patient.

Interesting, though. We do have all those samples and no one has any interest in looking, doing EM, on the small fibers. We have over 1000 pairs of sural-nerve biopsies.

DR. KATZ: Dr. Hertz, did you have a comment?

DR. HERTZ: I just wanted to ask if somebody could address, maybe at this point, the use of F-waves.

DR. FELDMAN: I am happy to, or David, do you want to? Or I can. It doesn't matter.

DR. CORNBLATH: For this question, none. There is no value. And, in general, they are just going to be another measure of long latency nerve function. They will parallel, or they should parallel, what is seen in perineal motor

conduction. They are a little bit more reliable in terms of a multicenter trial but, in terms of the kind of information that they give you intellectually, it is no different.

DR. KATZ: Just to be clear, you are saying that because they are not relevant to small-fiber function.

DR. CORNBLATH: That's correct. Can I try to answer this question and this is something I know Michael is going to talk about, I think one of the issues when we think about looking at small-fiber change, and I will use it as a global sense of the small-fiber change, I think we have to go back to this issue of what do you expect to change.

If you look at, as Eva suggested, cooling-detection thresholds, again, you are talking about the great toe and the question is, do you have a drug that could do this. If you don't have a drug that could do it, change at the great toe, it is a waste of time.

If you are talking about morphometry, the neurologic community is not going to allow bilateral sural-nerve biopsies. I believe they are unethical at this point in time. But the

skin-biopsy technique or a technique that would allow you to do quantitative sensory testing at another site with, for example, the Medoc device or another device that could be moved to a level on the skin where you would like to see sensory-function change, are going to be the wave of the future.

That is what we can do with skin biopsy doing morphometry, but you could do the same thing with a QST device if you could move it along the skin. A number of these are either available or in development.

DR. FELDMAN: You know, that is an excellent point and I just echo it a thousand times. I don't know, and Michael is going to educate us, if we can do--I know that Hopkins has done nice skin biopsy, using skin biopsies, in HIV drugs. But if we are at the point where we could use it in a large-scale trial for diabetes, it would be superb. It would be a superb measure for small-fiber function.

DR. KATZ: Just to push the QST point a little bit further, is there a validated procedure or any experience with using QST in such a way as to float upwards from the big toe?

DR. FELDMAN: No--oh, I'm sorry David. I was going to say no. All the validation with the Case IV QST has been done on the great toe or the forefinger. David probably knows more about the Medoc than I do, though.

DR. CORNBLATH: There are devices available that you can move. You could move Case IV. It would require a little bit of change in the sort of device, itself.

DR. FELDMAN: The design.

DR. CORNBLATH: You could move one of the devices anywhere and, as long as you did some studies that would show that you do it this way in every person, the same stuff you do for regular QST, you would have no trouble.

But it could be done easily. Is that right, Michael?

DR. FELDMAN: I don't think it has been done; is that correct?

DR. CORNBLATH: It has not been done on a giant scale. Individuals have done it.

DR. FELDMAN: I think it is an excellent suggestion.

DR. CORNBLATH: I think Mike has data on this point. He talked earlier about doing it on

the areas of postherpetic neuralgia. Michael--well, the two Michaels, Michael Polydefkis and Michael Rowbothom have both done it.

DR. FELDMAN: I would just say that, again, we have got the DCCT patient population. They want to do more for us. If we had the funding, we could do this on that population and couple it with nerve-conduction studies.

DR. KATZ: Ms. Delph, you were next.

MS. DELPH: You have suggested a number of primary endpoints which are basically surrogate markers. I think that it is important for us to have a good idea of how useful those surrogate markers are in terms of translating into clinical benefit. How useful are the ones that you have suggested, because if you don't have a good idea of what kind of clinical benefit you are looking at, then it is really difficult to weigh the risk-benefit ratio and efficacy versus toxicity.

DR. FELDMAN: So the clinical benefit that I would aim for in a clinical trial would be the halt the progression of the disease. So we can go back to the Rochester diabetic neuropathy study which is shown in the group of patients with neuropathy, just progression on a yearly basis, of

the NIS(LL)+7 and all other parameters they have looked at of nerve function and go to the DCCT which shows a progression--or, well, you can look at it two ways but essentially those patients with conventional therapy had a loss of motor-nerve-conduction velocity within a five-year period.

Those measures, those surrogate measures, do correlate at least with disease severity or intensity as monitored by clinical examination and more extensive electrophysiology testing, not by symptoms. So notice I haven't been talking about symptoms. I would be glad to talk about symptoms, but not by symptoms in these measures. So the measures I chose, one was a measure of where the patient stands clinically, so clinical efficacy, what is their sensation now in the great toe.

David makes a good point that that may not be ideal, but what is their sensation, let's say, in the foot or ankle region. What is a quantitative measure of their sensation, vibration-perception threshold. What is a motor-nerve conduction velocity, for example, and maybe a sural-nerve-evoked amplitude.

What I would maintain is that you take

that composite measure at Time 0, and if you have a successful intervention, I would maintain that that composite would stay the same. Maybe, if you hit the home run, you would get some improvement. In those patients treated with placebo, as we know this disease does, you would see the relentless progression of increased abnormalities in the components of that composite measure over time.

The reason to use more than one measure again is this isn't just a simple disease. You have got large fibers and small fibers so you need to be able to measure both.

MS. DELPH: I don't think you have answered my question.

DR. FELDMAN: Sorry.

MS. DELPH: At the end of the day, it is very nice to show improvement in conduction velocity and so on, and to show improvements in different size fibers and so on. But when you are looking at approving a drug, what is important is how does that drug, for example, affect your likelihood of developing ulceration. How much pain relief are you likely to get from it?

DR. FELDMAN: I understand.

MS. DELPH: From those endpoints, you are

talking about, it is going to be very hard, I think, without objective data to weigh the risk-benefit.

DR. FELDMAN: Let me take a step back. I understand better. What these data reflect, these abnormalities in nerve conduction and quantitative sensory testing is a loss of axonal fibers. I showed you that pathology at the very beginning. So there is data that correlates axonal fiber density with motor-nerve conduction, amplitude and vibration-perception threshold. Again, that is work by James Russell and Peter Dyke in, actually, the late 1980s.

There is a very nice correlation between loss of myelinated fibers and loss of these parameters. These parameters are simply our way of seeing how many nerve fibers there are. Then step 2 is, we know that, as you lose nerve fibers in the foot, those are the feet that are going to develop ulcers.

So these are surrogate markers to look for nerve-fiber loss, and it is nerve-fiber loss that eventually is going to cause ulceration. Does that answer your question? No? I'm so sorry.

MS. DELPH: What I am asking basically how

do you actually translate all of these surrogate markers into an adequate measure of clinical benefit.

DR. FELDMAN: Okay. The adequate measure, in my mind, of clinical benefit is halt of progression of the disease because if you halt the progression of the disease and you have measurable electrophysiologic parameters and measurable sensation, then you are not going to develop an ulcer. Those patients ulcers who lose all those parameters as they lose axons.

DR. KATZ: I think the question is that there is a philosophy that there should be a search for a patient-centered outcome at the end of the day and that nerve conduction to the patient, they don't know what their nerve conduction is. They know if they got symptoms, if they have trouble walking, if they are developing an ulcer, that sort of thing.

So I think the question is how does one, in a clinical-trial program eventually connect surrogate marker to the patient-centered clinical outcome or is there a need to make such a connection? Is that a fair translation?

MS. DELPH: I think, very simply, if I can

rephrase it, is if you get an improvement in conduction velocity or amplitude of X amount, that can translate into a decrease in your likelihood of getting an ulceration or this level of--on average.

DR. FELDMAN: So the data would be available to look at if you have a preserved nerve-conduction velocity, that means you have got this many myelinated fibers and you are very unlikely to get an ulcer. You can translate that, then, to having really no recordable nerve function, and on having no recordable or no visualized axons in a nerve biopsy and developing an ulcer.

But there is that jump there because they are surrogate markers of axonal function.

DR. KATZ: Dr. McCormick, a comment from you on this?

DR. McCORMICK: I think it may be helpful to think of your question in the context of other kinds of drugs that prevent disease even though, in this case, we are not preventing disease, we are preventing the ultimate course of the disease, for example, cholesterol-lowering agents or antihypertensive medications where you may not directly see the long-term effects of the change

but there is an anticipation and, in fact, data to suggest that certain complications of the disease will be prevented.

So I think that is what we are looking at here. The patients may not notice that they are not getting worse but we are trying to collect evidence that will allow us to draw that conclusion.

MS. DELPH: I understand that. But if you are looking at a cholesterol-lowering agent and an agent can lower your cholesterol by X amount, you have an idea of how much it is likely to lower your risk of a cerebral-vascular accident or a myocardial infarction.

What I am saying is if you have X change or if you have a quantifiable changes in these surrogate markers, in order to adequately weigh risk-benefit, the drug may produce nephropathy or different complications. What do you weigh, a complication and likelihood of developing nephropathy or something versus X amount of improvement in conduction velocity?

DR. FELDMAN: I think that, as we said--I understand now better what you are trying to ask and it is a very good question. There is a large

study out of the Veterans Hospital looking at the morbidity of diabetic neuropathy and also development of ulcers. It is actually a very highly morbid condition, so it is a high degree of patient morbidity.

And then it is the most frequent cause of hospital admission for a diabetic patient. That is an interesting and well-established fact. It is neuropathy and a nonhealing ulcer. As I mentioned earlier, 15, to some people say, 20 percent of all patients require amputations. So those are really the very end markers for all nerve-fiber loss.

I think what you would have to do is then measure the risk-benefit and the benefit would be if you could halt nerve progression. These are all the consequences of relentless nerve progression. So that would be what you would want to weigh, those two things. What we don't know is why some patients don't develop microvascular complications although they are poorly controlled.

DR. KATZ: One more comment on this issue from Dr. Bril and then we will go on to the next speaker.

DR. BRIL: There is work with the surrogates that show that if you have a certain

level of function in the surrogates, you are less likely to have foot ulcers and then you are much more likely to have. So if you have something that holds you in a low level, then the projection is that it will work in the long level.

That is not to say that a new drug shouldn't be tested once you have the effect on the surrogates, that it shouldn't be tested in longer-term studies. But the investment needed to show prevention of foot ulceration is a five-year trial. A lot of companies won't commit that kind of resource until they have some promising evidence in shorter studies.

I guess my comment on the scale question, clinical scales, too--I mean, even the clinical scales are made up of how patients perceive sensation. My own scale has symptoms in it, for good or bad. So these scales are based directly on the patient. They are not nerve conductions. They are not QST. They are how the patient perceives sensation and symptoms.

I think the basic thing we all agree on, although we may not agree on the right scale, we agree that scales summarizing clinical findings are important plus or minus other endpoints that we may

want to put in there. But, even the NIS, and Peter Dyke who started it all--I mean, we agree that they are all valuable.

The question is exactly what you should have in a particular scale. I am not sure we can determine that but there is a consensus that I can see that we feel that the clinical examination needs to be reduced to some kind of number that you can follow even though you might follow elements.

So, at the end of the day, we are not saying that this drug will reduce numbness or this drug will reduce pain, but it will reduce a composite score, a composite clinical score plus or minus other stuff, and we all seem to be convinced of that from what I have heard.

DR. KATZ: I am going to make a few enemies around the table who still have persistent questions and, despite that, go on to the next speaker. We have about an hour this afternoon devoted primarily to trying to better understand the meaningfulness of clinical outcome measures. So please accept that your comments in this issue will not be lost.

So Dr. Michael Polydefkis will speak to us about the use of skin biopsies in the evaluation of

peripheral neuropathy and neuropathic pain.

Skin Biopsies in the Evaluation of Peripheral Neuropathy and Neuropathic Pain

DR. POLYDEFKIS: Good morning.

[Slide.]

There has been a lot of talk about small-caliper nerve fibers and I am going to talk a little bit about skin biopsy which is a technique that has evolved over the past decade or so to look at this class of nerve fibers.

[Slide.]

So, as an outline, I am going to give some background as to where this technique came from. I will review the technique, itself, and how it has evolved into a clinical diagnostic test. I will review some of its use in clinical trials and how it has been used to study diabetic neuropathy and, potentially, to develop some novel outcome measures.

[Slide.]

So, first, small-fiber neuropathy sort of came to light of most prominence actually in a cohort of HIV patients who had prominent symptoms, most notably pain, in their feet and distal legs yet there was this paradox in that they were

relatively normal on exam. They had normal strength, reflexes, normal proprioception and normal nerve conduction and EMG test results.

They were clinically felt to have a small-fiber neuropathy but there was a relative absence of clinical tests to evaluate them. So that is where the beginning of looking into the skin for nerve fibers evolved and actually has its roots, again, in the Mayo Clinic where they investigated nerve fibers in the skin.

[Slide.]

This is a sural nerve. I show it to you just to emphasize that the nerves that I am going to be talking about, you actually can't even see here. The red arrow depicts a large myelinated fiber, the yellow a small myelinated fiber. But the class of fibers that I will be talking about are predominantly the small unmyelinated fibers which are C and A delta fibers which, again, you need electron microscopy to see.

[Slide.]

So, again, there is this size dichotomy but also a functional correlate. As we said, large-fiber nerves convey information about balance and pressure while small fibers convey information

related to temperature, heat, pain and pain sensation. Their loss or dysfunction really correlates with pain. So pain is the hallmark of patients with a predominantly small-fiber neuropathy.

[Slide.]

In terms of clinical tests, we have heard a lot about nerve-conduction tests. They are really a large-fiber test. You also have sural-nerve biopsy which, as we have heard, can also be used to measure large-fiber nerve morphometry. It is important to emphasize that small-caliper nerve fibers are invisible to nerve-conduction velocity testing. That is a point that has been made several times. Quantitative sensory testing can be used to measure small-caliper nerve-fiber function but, again, it is a psychophysical measure and it is important that the stress--I believe that it really requires vigilant patient cooperation and attention.

So, in the battery of QST tests they have done using the Case IV device, it is at least a forty-five minute procedure.

QSART, Quantitative Sudomotor Autonomic Reflex Testing, is a measure of autonomic

small-fiber nerve function and is a sophisticated device which I personally don't have much experience with. Also, sural-nerve biopsy can be used to evaluate small-fiber nerves but, as has been pointed out, you have to go to electron microscopy, another level, and it is quite laborious.

And now we have skin biopsy which I am going to talk about.

[Slide.]

We have learned that epidermal nerve fibers are predominantly sensory and they represent free nerve endings without Schwann-cell ensheathment. There are multiple neurological conditions with prominent small-fiber nerve involvement and many of these have been studied with skin biopsy.

[Slide.]

The technique, itself, is pretty straightforward. We use a 3-millimeter punch biopsy. This is what a typical biopsy, or four biopsies, look like. Typically, we shave the area but the biopsies heal by a process of granulation. There are on sutures involved. The risk of infection is nominal, on the order of one-half of

one percent including many diabetics.

[Slide.]

This is what biopsies can look like at two months. There is a mild scar.

[Slide.]

It is not uncommon at eight months to really be hard pressed to see any evidence of a biopsy although, in fairness, many people do have a mild scar that persists.

[Slide.]

I know it is close to lunch but if you think of skin biopsy as a loaf of bread, what we do is we section it and, from each biopsy, we get fifty-five sections, on average. We use 50-micron sections so you should get sixty sections. Clinically, at random, we select four slices, and that has been shown to give a representative sample of the whole biopsy.

[Slide.]

So, if this were raisin bread, by getting four sections, we get a representative number of raisins.

[Slide.]

Then we look at individual sections.

[Slide.]

This is an example. This is the surface of the skin and this is a section that is stained with a Panex solo marker PGP9.5 and these are the nerve fibers. The red line depicts the dermal-epidermal junction. So when a fiber crosses this junction, it is designated an epidermal nerve fiber.

[Slide.]

So, as we have said, most neuropathies, including diabetic neuropathy, is a length-dependent process and so we typically take biopsies from three locations; proximal thigh, distal thigh, distal leg. I will give you the example of how this is used to define life-dependent small-caliper neuropathy.

[Slide.]

This is a very proximal site, actually the back. But this is the normal, nonneuropathic individual. You can see there are plenty of nerve fibers. It is very well innervated which is what we would expect at a proximal site. Even the person with neuropathy, the epidermis is well innervated although, qualitatively, there are some abnormalities.

Again, this is what we would expect to

see. At a proximal site, we would expect to see innervation even in the neuropathy individual at a proximal site.

[Slide.]

Going distally, we are now at the thigh, we still have plenty of nerve fibers in the healthy person. In the neuropathic individual, there are still fibers but, again, morphologically, I think they are more abnormal, that we have swellings or fragmentations here. That is what we have taken over the years to be a predegenerative change.

[Slide.]

Now, at the most distal site, the ankle, and, again, the normal individual has preservation of innervation but, in the neuropathic person, there is a complete absence of epidermal innervation and the single fiber we see in the dermis, again, is fragmented. It appears to be degenerating. So that is how we have used this technique to define a life-dependent small-fiber neuropathy.

[Slide.]

Again, one of the strong suits of this technique is that it is quantifiable so, with a computer algorithm, we can measure the precise

distance and we can counts these fibers specifically to arrive at a density of nerve fibers per millimeter.

[Slide.]

The normative range has been established. So these are densities of normal people. I think it is important to point out that there is a healthy range of what is normal, but using the fifth percentile as the definition of abnormal, it is useful clinically with a diagnostic efficiency and specificity of 88 and 97 percent.

[Slide.]

I think it is also important to point out that if you biopsy many biopsies within one region, the measurement is very consistent.

[Slide.]

With training, you can have very high inter-rater and intra-rater reliability. Also, if you measure healthy individuals over time, if you serially biopsy one site over time, it is a very stable measure in a healthy population.

[Slide.]

So the Hopkins experience now totals over 7,000 biopsies including many diabetics. We typically do the three standard sites, as I pointed

out, and it has shown good correlation with QSART as well as sural-nerve biopsies.

[Slide.]

So a skin-biopsy technique has been used in a study of nerve-growth factor in HIV-associated painful sensitive neuropathy. This slide depicts some of those results. So I will focus at the distal-leg site, again, because this is a life-dependent process. The dark bars represent patients with severe or extremely severe pain while the dark gray is low to moderate pain.

It is the patients with more severe pain that are lower at distal-leg epidermal nerve-fiber density as measured by both the physician and the patient pain assessment. So this is consistent with the idea that loss of these fibers is associated with neuropathic pain.

[Slide.]

Also consistent with clinical observations is the fact that distal-leg nerve-fiber densities tended to be lower in patients with more severe immunosuppression. Again, that is consistent with the fact that HIV neuropathy is typically a disease of advanced HIV disease.

[Slide.]

So skin biopsy has been used by several groups to study diabetic neuropathy. This is a slide from Bill Kennedy in which he demonstrated that patients with increasingly severe diabetes have lower epidermal nerve-fiber staining.

[Slide.]

This is echoed in another study by Levy et al. in which they quantified epidermal PGP 9.5 staining in three populations; a normal control population, a population of diabetic patients who were normal by exam, symptoms, electrophysiology and quantitative sensory testing and the neuropathic diabetic population, and there seems to be linear relationship.

[Slide.]

Recently, there have been results of several studies looking at a precursor to diabetes in impaired glucose tolerance. Those studies have looked at impaired glucose tolerance in patients who otherwise have no known cause for their neuropathy. These patients, for the most part, prominently had pain as a feature of their neuropathy.

These reports are published at the University of Utah and Yale report roughly a 35

percent prevalence of impaired glucose tolerance in this population and that contrasts with a 15.8 percent IGT prevalence from the National Health and Nutrition study.

[Slide.]

We performed a similar study at Hopkins which is not yet published, but I will summarize it briefly. The results were very similar in that we found 36 percent of our patients with neuropathy of unknown cause were found to have impaired glucose tolerance and 20 percent were frankly diabetic. Again, that represents at two- to threefold increased prevalence above NHANES.

We also found that there was relation--the patient with the IGT-associated neuropathy had a less severe neuropathy than those with diabetes-associated neuropathy. So there was an implication that there is a dose-response relationship between the degree of glucose dysmetabolism and the degree of neuropathy.

[Slide.]

So the natural history of glucose dysmetabolism has been addressed by several large studies which have shown that impaired glucose tolerance is a risk factor for diabetes and

precedes diabetes and, based upon that, we hypothesize that the neuropathy associated with impaired glucose tolerance could be a precursor to diabetic neuropathy. Consistent with that was the observation that our patients' duration of symptoms in the IGT group was shorter than the diabetic group.

When we stratified patients by their fiber type, there seemed to be a sequential progression from small-fiber sensory involvement to combined small-fiber and large-fiber sensory involvement to sensory-motor involvement. So this argues that, at least in the population which we looked at, which is arguably a tertiary neuropathic population, that skin biopsy may be the earliest detectable sign of abnormality in these patients and have oral glucose testing might be a more sensitive marker of glucose dysmetabolism.

[Slide.]

We have also done some studies using skin biopsy to look at nerve regeneration in humans. I think the technique has several advantages in that it uses skin, which is easily accessible, it is easily biopsied and, as have heard, a sural-nerve biopsy is not trivial. Also, skin can easily be

rebiopsied. You can only biopsy sural nerves twice, one on each side. Skin is naturally regenerative and, as we have said, it is quantifiable.

[Slide.]

So we have developed two models to look at two forms of regeneration, regenerative collateral sprouting. I may touch upon that.

[Slide.]

So this is a measure of regenerative sprouting. This is a confocal micrograph which showed baseline epidermal nerve fibers. After injury, these fibers are completely eliminated from the epidermis.

[Slide.]

After recovery, this is 56 days, we see nerve fibers growing back. I believe this represents actual nerve growth and not an artifact of staining because we get the same results whether we stain with different Panex solo markers. It is also correlated with heat-pain thresholds.

[Slide.]

Collateral sprouting is another measure which we can measure nerve sprouting into a denervated zone. That is a different form of nerve

growth which has different neurotrophic requirements.

[Slide.]

So, conclusions; I believe that small-caliper nerve fibers are prominently affected in diabetes, or they may be, at least in some populations, the first class of nerve fibers to be affected. They have been relatively unstudied or understudied. I think that just points to the fact that the tools we have had to look at them have not been developed until relatively recently.

Their loss appears to be important in neuropathic pain and this approach offers the potential for an efficient way to measure nerve growth in nerve-regeneration trials.

Thank you.

DR. KATZ: Thank you, Dr. Polydefkis.

Before we proceed with questions for Dr. Polydefkis, we have a new arrival at the table. Dr. Dyke, would you care to introduce yourself to the group?

DR. DYKE: Peter Dyke, Mayo Clinic.

DR. KATZ: Thank you.

Questions for Dr. Polydefkis about skin biopsies? Dr. Dworkin?

DR. DWORKIN: Setting aside the issue of regeneration, I guess my question involves whether you think it is possible to use biopsies as an endpoint in the clinical trial. In other words, would one, in an early intervention designed to retard the progression of diabetic neuropathy, predict, with active effective treatment, less loss of epidermal nerve fibers in the treated group versus the placebo group, or my concern, based on the data you present is that this loss of epidermal nerve fibers occurs so early in patients with impaired glucose tolerance that it has not potential as an endpoint because it has already occurred before you would ever get these patients into a clinical trial.

DR. POLYDEFKIS: I think it is fair to potentially use it in a clinical trial. It was used in HIV although that trial didn't last very long. I think you can also vary the site. Like David Cornblath said, if you focus on the toe, you might be missing what is happening at the site of the neuropathy or the junction of the neuropathy and so, potentially, you could look at a more proximal site.

DR. KATZ: Dr. Farrar, you were next.

DR. FARRAR: With relation to Bob was just asking about, but also in terms of thinking about how to look at the data, I was struck by the slide you showed from Dr. Kennedy's work in the overlap between those three sets of figures.

I wonder, in correlation, then, with another slide that you showed which showed proximally there was no difference between the two biopsies between the two groups and distally there was. I wonder whether you, in fact, looked at the ratio between the number of nerve fibers in a relatively normal area versus a relatively abnormal area, whether that, in fact, helps to differentiate the groups to a larger degree.

DR. POLYDEFKIS: Right. So that has been done mostly notably by Chester MacArthur. That ratio can be helpful although, in general, we use absolute cutoffs. But if it is sort of on the border, obviously by looking at where it fits into that patient, you can put that number in perspective.

So if a person is borderline at the distal-leg site but proximally they have an abundance of fibers, that puts you toward saying it was more abnormal.

DR. KATZ: Dr. Bril, you were next.

DR. BRIL: Thank you. I think this is really an exciting field now. But I have a few questions that maybe you can clarify.

This is useful on those patients who have prominently small-fiber disease and, in the diabetic group, this would be early neuropathy in whom nerve conductions would be normal and a lot of the other clinical measures would be normal.

I guess my question is informational. So you have someone with burning feet, yet you have biopsied their ankle and more proximally. What does that mean to the burning feet? Which fibers--if you are losing fibers, what is signalling your pain, what is really carrying your pain forward? What is the relevance of the loss of these fibers in the skin at the ankle and more proximally to the burning-feet syndrome that we are dealing with mostly?

Usually, when the pain comes up higher, they usually have large-fiber involvement as well. So that is the thing. The Kennedy data, when I looked at that paper, and you look at the correlation with epidermal nerve-fiber density, it drops and then it is just at the bottom.

So, from a fairly--I mean, the mild patients, there may be a correlation, but you get moderate to severe, that is lost. I mean, it is just the fibers are all gone. They are not detectable anymore. So the reflection of the clinical state is a little, still, I think, early. So I would like your comments on that.

DR. POLYDEFKIS: First, the pain. I guess the question is what is causing the pain. That is an unknown. That is not known. But you are losing fibers from the epidermis but they are still there. The distal end is probably in the dermis.

DR. BRIL: But you would think in the feet, they would probably have more loss because you have got the gradient. You are not even doing the feet where they have the burning pain.

DR. POLYDEFKIS: Right. So just practically, we didn't biopsy feet because it is logistically complicated, increased risk of infection. People wear shoes. But I suspect you may be right. If you biopsy them more distally, you would see more severe loss.

The other question is that you are right. Once you get to 0, you can't go lower than 0. But you can biopsy more proximal sites. So, in more

neuropathic individuals, even though a distal-leg biopsy may not give you that much information, a distal-thigh biopsy might.

DR. BRIL: I guess the question, then, is if we are looking at nerve dysfunction up in the thigh and it is not related to the pain in the feet, how are we going to relate those two in a study, in an endpoint study, because we are going to have the same comment that we have had about other surrogates.

We are going to say, your nerve-fiber density is better in the skin and the thigh. But if the thigh is not even bothering you, if your thigh is perfectly normal, you can't detect a sensory deficit, there is no pain, the burning pain is all in the feet, you are going to have to answer the same comment.

DR. POLYDEFKIS: That is a fair point. That is why I kind of tried to point out some of the morphologic abnormalities. Even though patients won't have symptoms in their thigh, there is evidence of nerve injury in the thigh by the swellings and segmentations of the nerve fiber.

So I think you could argue that if you are improving a site, even though it might not be

symptomatically neuropathic, you are having an effect on nerves.

DR. KATZ: Dr. Rowbothom?

DR. ROWBOTHOM: Let me just make a few comments on that because we have been using skin biopsies to study postherpetic neuralgia and have published in this area since 1996. There you have a different situation in that you have a contralateral side that doesn't have clinical symptoms. It is not a perfect control because Zoster does produce some bilateral changes and so there may be some change in nerve fibers contralateral to the area of pain. But it certainly gets around the problem that you have in diabetic neuropathy where you have two feet that are deafferented.

What our studies show is that in the center of the area of greatest pain, that is where the nerve-fiber dropout is usually the greatest, if there is nerve-fiber dropout. As you biopsy towards the edge of the area that is affected, you get nerve-fiber counts that are closer and closer to what you see on the contralateral side.

The relationship between pain and allodynia, thermal-sensory function and the number

of fibers in the skin is quite complicated. In some earlier studies that we did, we found, actually, an inverse correlation between thermal-sensory impairment, thermal-sensory detection impairment, and pain so that it was the patients who had the best ability to detect thermal stimuli that actually had the most pain and the most allodynia which would suggest that it is not a complete loss of all the fibers that is necessary but that there is an important intermediate point where there are fibers there.

They are functioning, but they are not normal fibers. They are sick in some way. They are damaged and they can't fully recover. So the other point I just want to make is that patients who have no fibers left in their skin generally don't have allodynia to touch in postherpetic neuralgia. The ones who have allodynia, especially severe allodynia, actually do have a fairly--either a normal or near normal number of fibers in the skin in their area of greatest pain.

So that is a disorder where we can analyze the problem a little differently than diabetic neuropathy, but I just want to echo what David was saying earlier and also what Michael was saying is

that this is a technique that you can do serially and patients tolerate it well.

It may be a surrogate marker as far as quality of life or pain or other things, but it is a hard marker in that you actually are visualizing and characterizing the nerves. So if your agent is designed to be neuroprotective, you are actually getting real anatomical data about the physical state of the nerves that you are interested in.

DR. KATZ: Dr. Shafer, you were next.

DR. SHAFER: Two things. One is certainly what I have heard so far has been very positive in the sense that this is something that we have seen data now for diabetes, we have seen data for HIV-associated pain. You just reported data in postherpetic neuralgia, with the obvious exception of phantom-limb pain.

Is this something that, in fact, could be considered to be a broadly applicable surrogate for neuropathic pain?

DR. ROWBOTHOM: Yes and no in that there is not a perfect correlation between the number of nerve fibers and pain. That is really a major issue because the biopsy tells you how many fibers there are and, as Michael showed, you can make a

lot of inferences about morphology. But I think our state of knowledge about what we are seeing in the skin is still crude enough that we can't say that this biopsy picture guarantees pain and if you reverse that abnormality, then you have alleviated pain. We are not there yet.

DR. SHAFER: That actually goes right to the other thing I wanted to ask, then, was have you looked at counts of nerves versus pain as opposed to the morphological indices that we saw on the slides, and counts of abnormal nerves, dilated nerves, things like this, versus pain.

DR. POLYDEFKIS: It has not been looked at systematically. It is very challenging to look at that so you have to quantify what is swelling, what is a morphologic abnormality. So we have global impressions but, beyond that, it has not been systematically looked at.

DR. KATZ: Dr. Cornblath?

DR. CORNBLATH: We have done thousands of these biopsies in patients in our own place and I would echo what Mike said. It is not perfect. It is not going to be a correlate for this symptom. Some of that reflects the fact, as Mike said, that he has already shown that people have good numbers,

can have more allodynia, and it also reflects the fact, as we have talked about here multiple times, this proximal-distal gradient.

Our biopsies are done 10 centimeters above the lateral malleolus. That is our standard site. You can have your toes on fire and be really in a lot of discomfort and you can have a normal biopsy at that site because it reflects a morphologic change, then. So I don't think it would be useful unless you, again, started moving it all around and, even then, based on Michael's data, I am not sure it would work as a correlate of the symptom of pain.
It is a correlate of morphologic abnormality of the nerve.

DR. KATZ: Dr. Feldman?

DR. FELDMAN: Michael, could you refresh my memory on the David Hermann paper that showed--you mentioned in your talk, that actually shows that this is a good surrogate for sural-nerve biopsy. I mean, that, in a way, is very exciting if we could do these types of biopsies in lieu of sural-nerve biopsies and be able to do them separated in time and get similar or meaningful information.

DR. POLYDEFKIS: I can't recall the exact numbers but every patient who, on sural-nerve biopsy was felt to have small and myelinated nerve-fiber loss, that was in agreement with the skin biopsy and there were a few patients who had normal sural-nerve unmyelinated nerve-fiber counts who had abnormal skin biopsies.

It just spoke to the point that skin biopsy might be a more sensitive measure of that population than sural-nerve biopsy and that would make some sense because, again, skin is a more distal structure and so it may be consistent with skin being infected first.

DR. CORNBLATH: Again, we ought to be very careful because I don't think it is really a surrogate for the unmyelinated counts in sural nerve, and it isn't because there are people, as Michael said, in both the Holland paper and the Hermann paper, who have normal unmyelinated fiber counts in the trunk of sural nerve as we take it in the mid calf who have abnormal skin. That is perfectly predicable on the length-dependent nature of this disease. So it won't be a surrogate.

DR. KATZ: Are you saying, then, that it may, in some cases, be more sensitive than the

sural-nerve biopsy or is just a matter of--

DR. CORNBLATH: I believe so. But, again, that is all predicted on the basis that this is a length-dependent dying-back neuropathy and the sural biopsy looks at it like in the upper arm and Michael's technique and others look at it down in the fingertips where the action starts.

DR. KATZ: Dr. Woolf, you were next.

DR. WOOLF: I think you need to be extremely cautious about this because it is not a marker of nerve fibers. PGP stains are unbiquinase so it is not staining the nerve fibers. If that enzyme is downregulated, which it may be, or its transport is affected, which it may be, by the disease state, you will have an apparent disappearance of nerve fibers but the nerve fibers may be there or atrophic.

So I think we have got to be a little bit cautious about that in the same way that I think we have got to be extremely cautious about correlating the entire experience of pain with peripheral-nerve endings where so much of pain is centrally generated by altered processing in the CNS.

DR. POLYDEFKIS: I think that is a good point. I should say if you use other Panex solo

markers we see the same thing. So I suspect the conclusions may well be correct.

DR. CORNBLATH: We have looked at EMs in skin when the PGP 9.5 is not there and the fibers are not there.

DR. WOOLF: I have no difficulty with that, but that doesn't mean that every time--I am sure that if there are no fibers there, you will have no PGP. What I am saying is can you do the other way around, just because PGP is gone, can you be always confident fibers aren't there.

DR. CORNBLATH: In the cases, and we haven't done thousands of them because, as you can imagine, they are technically difficult, when there isn't PGP 9.5 staining, there are not nerve fibers, if that answers the question. That is, we have not seen cases where the PGP stain is absent--

DR. WOOLF: I think Frank Rice has an experience where the fibers can get so thin and atrophic that, on thick sections like 50 micron sections, you may not get staining but, in fact, when you reduce the size--this is getting into technical issues, but if you increase the sensitivity, you can start to see very thin atrophic fibers.

DR. CORNBLATH: I would be interested to see that material.

DR. KATZ: Dr. Farrar, you were next.

DR. FARRAR: With regards to the comment about pain and the central processing, I think it is important to point out two features of diabetic neuropathy that are paramount in terms of thinking about how to treat the discomfort.

The first of the features is that the improvement that we are looking at is in the peripheral nerve. I think it was commented earlier that if the peripheral nerve becomes enough, you actually get damage to or potentially death of the cell body at the dorsal-root ganglion.

My guess is that if the cell body dies that the nerve doesn't come back, in general, anyway. Once that has happened, any amount of trying to control the process that caused the nerve to die originally is not going to help. I guess the analogy is once the car has crashed into the tree, fixing the brakes doesn't help very much.

The second issue I think is that the process we are talking about in terms of this disease is really a peripheral process and we know, as Clifford was alluding to, that some of the

treatments that we use don't work peripherally at all but, in fact, work centrally to increase the downregulation of changes that occur at the spinal cord. So you might see a drug that works very effectively in a symptom--i.e., control of the pain--that has no effect or no benefit on the peripheral system.

I think that is the problem in trying to look at these two things together. Clearly, preventing the progress of the disease is a good thing and probably, ultimately, results in changes in sensation and/or pain discomfort, although I think I agree that it needs to be clearly demonstrated. Some of it has been.

But, in addition, there are going to be agents that don't work at all peripherally that would be clearly beneficial for the symptoms. Would you agree?

DR. POLYDEFKIS: Yes.

DR. KATZ: Dr. Dworkin, you have the last question.

DR. DWORKIN: We have talked a lot about using skin-punch biopsies as endpoints. I was wondering if you could comment on their potential use as part of the inclusion criteria for a study.

In other words, could you imagine a study of idiopathic small-fiber neuropathy where that would be an inclusion criterion, that the patient has small-fiber loss? Is there a role there?

DR. POLYDEFKIS: I believe so. I think it is also potentially would support some of the scales that have been discussed.

DR. DWORKIN: As part of the composite.

DR. POLYDEFKIS: Right.

DR. KATZ: I would like to end with just one final question. One thing that I may have missed in your talk is that has the skin-punch biopsy neurofibrodensity been followed longitudinally in a patient population to look at what magnitude of change one sees?

DR. POLYDEFKIS: We are doing that but it has not been done systematically. We are in the process of doing it.

DR. KATZ: So it would seem difficult to put that on the top of the pedestal as an outcome measure without that experience of looking at the degree of change that occurs. Do you agree with that?

DR. POLYDEFKIS: I think that is fair; yes.

DR. KATZ: Lunch now. We will start promptly at 12:55. For people around the table, head to the back of the restaurant next door and everybody else enjoy your lunch. We will see you at 12:55.

[Whereupon, at 11:55 a.m., the proceedings were recessed to be resumed at 12:55 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1 o'clock p.m.]

DR. KATZ: We will start the afternoon session. This portion of the afternoon session will be devoted to discussion of some of the critical issues in relation to clinical trials for diabetic peripheral neuropathy. In order to help us focus our attention on exactly what those questions are, Dr. McCormick will give us a charge to committee.

Charge to the Committee

DR. McCORMICK: Welcome back. This afternoon, we will bringing to the committee a number of issues that have been challenging both the FDA and industry as we approach the development of drugs for neuropathy and neuropathic pain, as you have heard this morning.

You have heard also this morning a bit about the regulatory context in which we operate, the need for a delicate balancing act and thoughtful judgment as we apply new scientific ideas and knowledge within our regulatory framework.

We will be seeking advice from the committee this afternoon on a number of questions.

Keep in mind that our regulatory approval and policy decisions must be based on evidence. Neuropathy is an area of drug development in which there has been a paucity of evidence generated. The elements that go into the design of clinical trials and drug-development plans should be widely accepted by experts in the field.

We will be asking your advice on outcome measures, usefulness of surrogate endpoints, duration of trials, effect sizes that are clinically meaningful, and appropriate definition of entry criteria which will help to define the drug's indication.

As for neuropathic pain, the most commonly considered question is do we know enough to generalize yet. There are some clear benefits to industry, as we have heard, in obtaining a broad indication for neuropathy pain. If and when this is something we should consider, we should carefully think through what evidence would support such a broad indication and be able to articulate why; that is, justify it, keeping in mind that policy steps that are taken with one class of drugs may adversely affect another.

We would like to hear some discussion

about how much existing data you feel you have in making generalizations about drug effects across the vast variety of neuropathic-pain states. You should also consider the risks associated with a broad indication such as the risk of overgeneralizing based on a narrow set of data or insufficient safety exposure in the target population or, in the case of some narcotics, widespread availability and prescription-drug abuse.

These risks would ultimately have to be addressed by us before and as we make an approval decision. Keep in mind that if the FDA allows a broad claim for a given indication, we must have sufficient evidence that such a claim is really applicable, the truth-in-advertising principle.

There is also a down side to a narrow indication based on a small development program particularly if the drug may have a much larger target population. The greatest risk of widespread off-label use is that of inadequate safety evaluation during development. There are the additional problems with reimbursement which has plagued the neuropathic-pain community.

You have had a chance to read the FDA's

guidance for providing evidence of effectiveness for human drug and biological products. You can see from this document that there is some flexibility in the evidence that can be accepted in support of efficacy. This flexibility increases as experience is gained with a class of drugs or indication.

Keep these principles in mind as you enter your discussions this afternoon. The afternoon will be divided into discussions of neuropathy drug development, disease-altering claims and the second half will be discussion of neuropathic pain. A debate on the issue of general versus specific claims in neuropathic pain will hopefully stimulate your thinking.

We are grateful for your willingness to share your expertise with the FDA and we look forward to a stimulating and very fruitful discussion.

I won't be going through the questions since there is a long list of questions but I will defer to the chair to go through them one by one as we move forward through the afternoon. Thank you.

DR. KATZ: Thanks Dr. McCormick for setting the stage for this afternoon.

What I would like to do first is, there were a number of people in the room whose names were mentioned several times by speakers as having relevant experience and expertise to share with us who are not sitting around the table. I would like to sort of reopen in a small way the public forum by asking any of those individuals in the room who might be there, Mitchell Max is one and Joe Arezzo is second. So, if you could just take two minutes, Dr. Max.

DR. MAX: Mitchell Max from the National Institutes of Health. I just need to say that my conflicts of interest include that I either collaborate with or consult for a large proportion of the companies doing analgesic drug development.

I wanted to mention some very odd phenomenon, and it is an important public-health need, that the neuropathic pain condition that is by far the most common has hardly been mentioned today. We have been talking mostly about diabetic neuropathy and a little about postherpetic neuralgia, but there are ten to twenty times the number of people with pain from nerve root, from degenerative disease in the neck or the back.

It is very odd that there are essentially

no academic NIH-funded drug-treatment trials in chronic radiculopathies and there is essentially no industry development. I would urge you, since that really is the bulk of the difficult neuropathic pain we treat, just think of how many people in your family and your close friends have complained to you about sciatica or neck pain, or yourself.

Since this is so important, we ought to think about how we can promote it. I must confess that every drug company I have ever spoken to, at the beginning of the meeting, I say, why don't you, if you want to neuropathic pain, do a clinical trial in radicular pain. And they always reject it and they say no, we are going to study diabetic neuropathy even though all the other companies are going for that because there isn't any track record yet. They are afraid that maybe it won't work. There is somehow this strange hurdle.

Another point that perhaps you can discuss later, it is not clear to me that results in diabetic neuropathy and postherpetic neuralgia generalize to root pain. In root pain, there is generally mechanical pressure on the root or on the dorsal-root ganglion and the biology of pushing on the nerve cell or the root which is central to the

nerve-cell body. The biology must be different from an injury peripherally, so maybe you need to do separate trials in that.

So I would just urge you to think about how you could encourage by a claims structure or some other thing companies to get into radiculpathy pain so we can treat what people have.

DR. KATZ: Thank you, Dr. Max.

Dr. Arezzo? Also, if you could start with any relevant disclosures, that would be helpful.

DR. AREZZO: I am Joe Arezzo from Albert Einstein College of Medicine. I have consulted with many of the companies in terms of diabetic neuropathy and a few in painful neuropathy.

I think one of the more intriguing questions raised this morning was the issue of what is the relevance of the surrogate endpoints, a question that you posed, what does it mean to the patient to have a change in nerve conduction, particularly a relatively small change that might be seen in a clinical trial or a change in quantitative sensory testing, does that have impact for the patient.

I think we have obviously limited data in that respect as many of the people have already

mentioned. But one of the more important studies in the DCCT trial. In that trial, essentially a 1-meter per-second per-year change in the perineal nerve-conduction velocity translated to the 50 percent reduction in clinically evidence neuropathy at the end of a five-year period of time.

So patients that experienced--that were intensively treated and had 1 meter per-second improvement per-year had 50 percent--there was a 50 percent difference in the clinically evident neuropathy at the end of five years in terms of the number of patients.

Another study that I think is relevant is Andrew Bolton's study and Jay Sosenko's studies on quantitative sensory testing. Andrew Bolton for vibration demonstrated that elevation of vibration, quantitative sensory-testing scores to a threshold that he defined as important, 25 volts in a biothesiometer, had more than a fourfold--if you elevated to that score in quantitative sensory testing, you had more than a fourfold increase in your incidence of ulceration of the foot.

So that was a threshold, a point which you could measure in patients before ulcerations but a point which was very strongly predictive of those

patients that would have ulcerations.

Jay Sosenko did a similar study with thermal thresholds demonstrating the relationship between progression of quantitative scores to an area of risk and the clinical development of ulcerations. So these surrogate points are clearly surrogate measures but I think they do have direct relevance for the progression, the long-term progression, to serious clinically relevant neuropathy.

Thank you.

DR. KATZ: Thank you very much, Dr. Arezzo. Is there anybody else from the public that would care to take the opportunity to share some thoughts with us?

Okay, great. Why don't we go ahead and start the discussion then.

Entry Criteria

DR. KATZ: As you can see in your agenda, the first topic that we will be focussing on this afternoon is the topic of entry criteria for clinical trials for diabetic neuropathy. Again, just to focus everybody's attention, we are not talking about pain right now. We are talking about disease-modifying drugs and trials of those to

interfere with the natural history of peripheral neuropathy.

After we discuss the entry criteria, the next subject will be outcomes measurement and so it will be very easy for us to slip into that. But I would like to try to avoid that for now and just talk about entry criteria per se so we can accomplish something in that domain.

Now, of course, there are a number of relevant questions in terms of entry criteria for patients with diabetic peripheral neuropathy. Why don't I take the prerogative of just starting off our conversation this way with how one should make the diagnosis of diabetic polyneuropathy in such a clinical trial.

Any thoughts on that issue? Dr. Feldman, you look like you are nodding your head there and a thought is percolating. Would you care to start?

DR. FELDMAN: I think that the diagnosis needs to be made on a clinical ground in terms of some sort of clinical examination. We talked earlier about potentially a modified NIS(LL) or potentially the quantitative, semi-quantitative sensory testing that David does up the leg in his type of examination or ones that have previously

been developed by myself or Dr. Bril.

But the key is we need a clinical portion of the examination and that needs to, then, be accompanied by, I believe, a quantitative portion because all electrophysiology and quantitative sensory testing is just an extension of our clinical exam. So I would say that a nerve conduction study focused on the perineal motor nerve and the sural sensory nerve, and then possibly, depending somewhat what your entry criteria are somewhat are dependent are what your outcome measures are, of course, because, for example, if you want to measure changes in cold perception threshold, then you are going to need, as an entry criteria--or vibration perception threshold, you are going to need that to be measurable upon entry.

I do believe that the sural and perineal need to be measurable upon entry. So I think that patients meeting those three criteria would be good candidates for a clinical trial.

DR. KATZ: Just to state what probably is obvious, is it obvious enough that it is widely accepted that a clinical evaluation, by itself, is insufficient to characterize patients on entry to

such trials and that the quantitative testing is required?

DR. FELDMAN: I think the DCCT is a great example where, in the DCCT, a neurologist examined the patient. Although there were specific things you were to do at the end of the day, it was whether or not the neurologist said yes or no, you had neuropathy. It wasn't totally nonquantitative.

I think, though, because of somewhat of the subjective components of the clinical exam, I think a simple clinical examination probably is not sufficient for entry into a clinical trial. Certainly, it is very sufficient in the clinic. I am sure it would be good to hear what Drs. Dyke, Cornblath and Bril think about that, but I do think you need to extend your clinical examination with something more quantitative.

DR. KATZ: Dr. Dyke, do you have any comments on that?

DR. DYKE: I agree that, for a trial, you really would want objective criteria. I have thought that that nerve-conduction attributes are very good for that purpose and I agree that the quantitative sensory could also be.

If I could digress a little bit more,

though, and broaden this a little bit, it is important for us to recognize that the assumption around this table has been only about diabetic sensory polyneuropathy. But that is only one of a series of other neuropathies.

So one, in thinking about entry criteria, ought to say what neuropathy we are talking about. There are diabetic sensory polyneuropathies. There are some of them that begin during the honeymoon, if you like, called insulin neuropathies. They may have a totally different pathogenesis than the metabolic polyneuropathy.

So there probably are different diabetic sensory polyneuropathies. Then there are multifocal neuropathies and entrapment neuropathies. The median nerve at the wrist, the ulnar nerve at the elbow are two common examples, but the perineal is the third.

Then there are multifocal motor neuropathies of several well-defined characteristics. Osh described a brachial-plexus neuropathy form. There is a well-known lumbar form, thoracic form, if you like. And then there is the lumbosacral form.

The putative mechanisms are quite

different. So, in my mind, one has to begin with neuropathy we are talking about. Are we doing a preventative or an interventative trial? What pathophysiology are we going after? It could make a big difference.

So I don't see this as something this group can tackle just broadly as we are doing here now but I think you would have to specify first that we are probably talking about the metabolic variety. We are talking about diabetic sensory polyneuropathy. If that is the criteria we are using, then it makes sense, I think, what you said.

If I could just mention two other things. It also depends on the putative action of your drug. There really is a need to think of trials that address different issues. Clearly, there is a metabolic basis for diabetic neuropathy. I think everyone agrees with that, but there could well be a mechanical basis for other varieties, an immune basis for still other varieties, a hypoglycemic anoxic basis for others and so on.

Then I think it also depends, in terms of criteria, about the outcomes, but you want to leave that for the next one. But I did want simply to say we really ought to broad the idea of pain

because diabetic neuropathy has more than pain. They have positive neuropathic sensory symptoms which consist of lancinating pain, burning pain, deep aching pain, itching, tenderness of their feet when they walk.

The people who propose the study need to think about those things and it would really modify the criteria. So I think it would be a mistake to come down with a sort of rigid set of criteria for an undefined study on "diabetic neuropathy." A little side pitch.

DR. KATZ: No; that is clearly important. Let me just push you a little bit on that. It sounds like you are saying that if one is trying to study the metabolically based peripheral diabetic polyneuropathies, stocking-and-glove neuropathy, that one ought to take pains to exclude other kinds of neuropathies associated with diabetes, multiple-nerve entrapments, thoracic radiculopathy, proximal neuropathy, et cetera, et cetera.

How would you suggest operationalizing that attempt to exclude those other diabetic neuropathies in a clinical trial?

DR. DYKE: It would be clear that you could have an algorithm in which the neurologist

ends up making the final judgment. One could do it having the nurse call and determining some things and then going on to the neurological examination as proposed by Dr. Feldman.

I think the bottom line is, though, that there really are differences even in the diabetic sensory polyneuropathy and we really ought to focus. If you are going to set down criteria, you ought to focus on which variety you are talking about.

DR. KATZ: Are you suggesting, then, that even among the stocking-and-glove neuropathies, polyneuropathies, associated with diabetes that there are different physiologic subtypes there that can be distinguished in some way?

DR. DYKE: We think so. That needs to be established but the Columbia group did nerve biopsies on patients with diabetic neuropathy and found that there were certain ones that had inflammatory infiltrates. We found the same thing. We think that the patients who don't have tripathy--that is, retinopathy and nephropathy, or mild degrees of that, and have a lot of symptoms, that immune factors might, in fact, be playing a role in those.

So that needs to be taken into consideration. So, for most of the trials that I am involved with, we have always said patients should have diabetes by ADA criteria. Secondly, they should have stable metabolic control. Three, certain categories of disease should be ruled out, like other diabetic neuropathies.

6 to 8 percent of a diabetic cohort have other kinds of neuropathy. If you don't put them aside, you are mixing up the trial. Then you go on from there to exclude patients with overlapping neurological disease. If they have Freidreich's attacks in addition to diabetic neuropathy, you are not going to be able to tease it out. So other neurological diseases need to be sorted out.

Then the question of what degree of metabolic control should they have before you put them into the study. The ADA criteria now hold that you should try and be--you know, people in the audience should know this much better than I do--below 8 percent on the glycated hemoglobin or maybe even on the hemoglobin A1C.

Now, on the other hand, you don't want to exclude such patients from trials if they can't get that level of control. But that is a big area of

concern. If they have, in addition, a little uremia, the uremia, itself, can cause neuropathy so that has to be a factor that has to be considered.

So it is a very complex issue, actually, the inclusion and exclusion criteria. But I think it begins with a clear focus on what you are trying to improve and that makes a big difference.

For example, one drug might affect--you might be aiming at the symptomatic group so you clearly have to pick Stage 2 patients. Other patients, you are trying to influence impairments so you have to have a milder group that you are studying.

Well, I have spoken too much.

DR. KATZ: You have hit on a lot of critical issues that I am sure we will discussing at length and I appreciate that. What I would like to do is just summarize some of the key points you made for the purpose of moving the discussion, focussing the discussion.

It sounds like what you are saying is that, number one, for patients to be included in a clinical trial for distal sensory polyneuropathy and diabetes that, number one, we ought to exclude other types of diabetic neuropathy and there should

be some sort of algorithm or operation or proviso that requires a neurologist to exclude those other diabetic neuropathies.

Secondly, it would be important to exclude a nondiabetic cause of a peripheral polyneuropathy such as vitamin deficiency, alcohol, what have you. Those points seem clear enough although, in my experience reading results of clinical trials, it is not usually done.

Third, we have to be careful in accepting patients with uremia which may be due to diabetes into the trial or at least potentially look at those patients differently. Fourth, there may even be subtypes within what we usually lump together as diabetic sensory polyneuropathy that, although we don't have any technology now to tease those different subtypes out, there may be ways of approaching that that we ought to keep in mind, one being potentially tracking which subgroup of patients has nephropathy and retinopathy since they may be different than patients with neuropathy that don't.

Have I captured everything you have said as far as the entry criteria?

DR. DYKE: Maybe also add the point that

try and use as objective a criteria for entry as you can. Usually, that means based on a normative study in which it is defined as an abnormal percentile.

DR. KATZ: Does anybody have any comments specifically about the proposals that we have just had put on the table with regard to entry criteria? Dr. Rendell, you have been waiting for a while.

DR. RENDELL: Dr. Dyke wasn't here this morning when I raised just this question. The question is, Peter, do you think there is a way to tease out subtypes of what appear to be the same disease--in other words, diabetic sensory polyneuropathy--and, specifically, do you think there may be certain individuals who have microvascular disease as the genesis of their neuropathy, others who have excessive oxidation as the genesis, others who have abnormal aldose reductase? Is there any way to get at a possible multiple heterogeneous etiology and then be able to select drugs that might treat one or the other subtype?

DR. DYKE: I can't answer it in any final way but I think the consensus is growing among many of us that, from the time of the studies at Arhus,

Denmark, where they showed an association between retinopathy and neuropathy and nephropathy, and there have been many studies since that time, that there is, in general, an association.

If you don't, in a given patient, have this association, you may not, in fact, be dealing with the metabolic diabetic polyneuropathy.

The second trend that I think we are seeing that people are recognizing that there may be other mechanisms that influence the expression of generalized neuropathy. One of them is, obviously, immune events. I was suggesting that the sort of insulin neuropathy that people talk about where it actually was described from Michigan in 1945 where a person who gets put on insulin develops a symptomatic neuropathy and then, six weeks later, improves.

That is common experience. They are referred to by the Brits as insulin neuropathies. I am not sure what that is. It could be metabolic but it could also be immune. One should be careful about that, I think, as a subgroup. So, most of us, in our thinking about trials have tried to keep that group out of it because we don't know what is causing it.

Then, clearly, you know the compression neuropathies are a real confounding variable in trials. Perkins and Vera Bril and someone else just wrote an article in which they were looking at this question, can you tell the difference in the electrophysiological features of patients who have both clinical carpal-tunnel syndrome and diffuse neuropathy versus polyneuropathy.

They said, in their equation, that they were not able to show a difference. I would like to suggest a few things to your study, Vera, but that can be done later. But the point is well made. It is hard to separate out the electrophysiological features which are from carpal tunnel and which are from diffuse neuropathy.

Then there is that whole group of the radiculoplexus neuropathies which is coming in like gangbusters. There is no question there is an immune component. So I think, at certain levels, one can do it.

DR. KATZ: Dr. Bril, would you like to make some comments?

DR. BRIL: I would agree totally with Peter. We have to define the type of neuropathy we are planning to study in any research trial. That

is fundamental. I agree with Eva, you do need some clinical features buttressed by objective measures, electrophysiology plus or minus QST. I think those are essential and they have been successful in selecting populations.

I think what was interesting was that there was no good electrophysiological measure to differentiate the patients because, if you want to get picky about it with electrophysiology, you can almost eliminate everybody with diabetic neuropathy as having carpal tunnel and then you would never have a patient in your study.

The reason we were trying to do this study was to see if we could--various algorithms have been suggested to me over the years such as the difference in median sensory to ulnar sensory, the difference in the amplitude ratio from the median to sural, from the median to ulnar, a difference with a proximal conduction to the distal conduction.

Yet multiple different electrophysiological rules to try and separate carpal tunnel in someone with diabetic neuropathy from the diffuse neuropathy had been suggested as exclusionary rules. None of my colleagues knew

which was the best one. Everybody had a little different rules.

The purpose of the study was to look at patients with diabetes, look at who had clinical neuropathy to find clinically in the way most neurologists would do it, and then see if you could separate those patients out from those with neuropathy by electrophysiology, and you couldn't. You just couldn't.

You couldn't do it in those with diabetes without neuropathy. You couldn't do it with neuropathy. So, if you want to exclude those patients from the studies, it is not too rational. Certainly, you can't measure outcomes on the basis of hand symptoms, but the electrophysiological studies don't do the job. Therefore, you become exclusionary in a research trial, and this was the only caution I had.

Definitely, you don't want to mix lumbosacral plexopathy with a diffuse sensory-motor polyneuropathy. Definitely, you don't want someone who only has hand symptoms and no other evidence of neuropathy at all. That is why you have the rules.

But I am not sure that someone with carpal tunnel, for example, should just be eliminated.

Now, this is really fine detail for this committee but that was the purpose of the paper. And yes; I would like to do a prospective study and find a good electrophysiological measure so that we could send patients back to the neuroconduction lab.

At this stage, I basically give them a trial of therapy. I am not very convinced of any good measure.

DR. KATZ: Dr. Bitetti?

DR. BITETTI: I wanted to make a comment that I think that how the drug gets labeled is going to be relevant to the entry criteria in some ways, too, because it seems to me that if we are going to have very, very narrow entry criteria, because we are now telling industry how to set up a drug trial, that the more narrow we make it, are we then going to only give them a label for that very, very narrow section of this type of diabetic neuropathy.

I know I am jumping ahead, but depending what we decide about broad versus narrow labeling, I think that drug companies certainly want to think about whom they are entering in their original studies if that is going to determine whom they get a label for.

DR. KATZ: Is there a regulatory perspective on that issue?

DR. McCORMICK: There is no question that the entry criteria that you set forth and use for your clinical trials has an effect on what you have in your label but I guess the question that I would turn back to the committee would be how relevant do you think, or how extrapolatable do you think, the more narrowly defined population would be to the general population of patients with diabetic neuropathy.

DR. KATZ: Dr. Foster?

DR. FOSTER: I simplistically liken this in study design to a football field where, on each side of the field, you have got the yard arms. How wide those goal posts are going to be for the entry criteria and how wide those goalposts are going to be for the exit criteria for an evaluable patient I think is something that the agency needs to think about from the standpoint of the nature of this disease, the amount of drugs, all of the issues, the comorbidities that we have talked about this morning, so that we wind up with studies that are generalizable to a broad population of folks but that subset analysis done on the other end of the

field after the study is over, post hoc analysis--and there are designs that will accomplish that.

So it would seem to me that what I have heard this morning, not being a neurologist, is that there may be a multifocal scoring system that would involve both subjective and objective criteria for entry and a scoring system that would be agreed upon by the investigators for at least pre-inclusion of those folks.

So, they might be Level 1, 2, 3, kind of like a New York Heart Association classification analogy. Then there would be a post hoc subset analysis, but being able to move the goal posts on both sides. I think those types of designs are important to consider with a disease like this that is so multifactorial.

DR. KATZ: Dr. McLesky?

DR. McLESKY: I would agree with everything that has been said. In fact, obviously from an industry perspective, we would like the broadest claim that is reasonable. In fact, if we limit the enrollment criteria or tighten it down so, so finely, would the generalizability be lost, number one. On the other hand, the tighter the

enrollment criteria, the greater the likelihood we will actually be able to show a result.

On the other hand, the tighter the criteria we have, the slower the enrollment potentially would be which is also adverse. So it is a delicate balance between the two extremes.

DR. KATZ: Dr. Dyke?

DR. DYKE: Yes; I agree. You know, an indication that I thought makes sense is that for the metabolic diabetic sensory polyneuropathy, the aim is prevent or ameliorate the symptoms and impairments of diabetic polyneuropathy. That is broad. And that is doable, as I see it. And that is measurable because you clearly have, then--and by impairment, I mean, broadly, impairment, neurological signs, nerve-conduction abnormalities, other tests of abnormalities.

What we are all looking for is an honest-to-god effect. If one really could prevent diabetic polyneuropathy, even the first five yards, hopefully, the next fifty yards would be preventable also, or if we could turn the direction of neuropathy from worsening to holding the same or even improving, that is what we want.

So I think most of us are looking for

really hard evidence that a drug is efficacious. Does it really affect the development or the worsening of symptoms and impairments taken broadly. My concern is, though, that for regulatory purposes, they must not make the shoe fit all persons or all diseases, was the point I was making, not to diminish the scope of what we are trying to do.

DR. KATZ: There is a question hanging in the air and I just want to make sure that we address it. Obviously, a drug that is effective for hypertension is not effective for every person with hypertension and a drug to lower your cholesterol is not effective for every person with high cholesterol. So, given the fact that no matter what disease a drug is effective for, it doesn't work for everyone with that disease.

Do people around the table feel that it would be inappropriate to conduct trials in patients with well-defined diabetes polyneuropathy and not cranial neuropathy and radiculopathy and vitamin deficiency and those sorts of things? If those trials showed efficacy, do people around the table feel that it would be inappropriate, then, to label the drug as being efficacious for diabetes

polyneuropathy or is that too inappropriate a leap? Specific comments about that question?

Dr. Farrar?

DR. FARRAR: Dr. Katz, what you have done is to say what is the question again. I think the issue, if you want a broad indication, then you have to show that your drug works in the population that it is intended to work in. I agree with what Dr. Dyke has said about the potential differences in the underlying mechanisms for the disease.

On the other hand, there are two ways of approaching it. One way is to look for only that segment of the population, test your drug only in that segment of the population. It probably costs a little less although enrollment will be a problem.

But if you only show it in that one segment, then I think there is a reason to believe that you should get a label for only that one segment. What would make much more sense is to do something along the lines of what Dr. Foster was suggesting but post hoc suggests that you think of it later and do it later.

I think you actually plan the study with the intent of looking at the global outcome in your

entire group and then you specifically state in your goals that you are going to look at the various subsets. If it turns out that your drug only works in one of those subsets, then that is the subset it should be used in.

If it turns out that it works, as you have suggested, in sort of the same number of people but in each of the various pieces that you want to divide it into, then you get a general indication because, as you say, not every drug works in every person.

I think there are just some very clear ways to approach it that make sense, and the same with other diseases. If you have got different kinds of hypertension and your drug works in all of them, then that's fine. If it doesn't, then you should use the specific one.

The last thing I think that is important is that there is a lot of concern about inefficient trials if you have lots of different potential etiologies and you end up with relatively small differences between your groups. That is very true if you insist on a mean value.

But there are ways to look at the data which cost only a very little bit in terms of the

number of patients you need that actually allow you to find very small differences between groups without huge numbers, and it has to do with the way in which the analysis is conducted.

But you need to decide a prior what you are going to do and then you need to do it. I think whichever mechanism you pick, you ought to get a label appropriate for that.

DR. BRIL: Before we go far with the splitting, I need to ask Peter and, perhaps, you, how you are identifying these subsets. When I see my patients, maybe sometimes they don't have much retinopathy or nephropathy but they usually have a bit. I am not seeing these subsets so clearly in my clinical evaluation, my nerve conductions or QST, the things I can measures.

Sometimes, yes; they have just gone on insulin. They have insulin neuritis. I agree with that. That is really rare. The common patients I see, I can't split yet. Can you split them for us?

DR. DYKE: No; I didn't want to go that far. I think, obviously, we shouldn't think of ocular-motor neuropathy as a component of diabetes sensory polyneuropathy. Yet, in many industry trials, you know, from being a reading and

quality-assurance center, a lot of diabetologists say it is diabetic polyneuropathy. They just lump it together and I think we shouldn't do that.

And we should make clinical distinctions of carpal-tunnel syndrome and ulnar neuropathy. And you do that at a clinical level. I don't think you and I would differ on that.

The difficult ones are the sensory polyneuropathies from coexisting causes which does happen. It has happened to me. I have had a patient in a trial and, four years later, I have discovered that her brother had the same sensory neuropathy and so, clearly, there was at least the possibility that that sensory neuropathy was inherited.

All I was saying is that it may turn out that, even in the sensory polyneuropathy group, there may be different causes and if we can pick them out, we should try to do that.

DR. KATZ: Dr. Cornblath, you were actually on deck next. Do you still have a comment?

DR. CORNBLATH: I keep going back to what was said very early which is we are sort of putting the cart before the horse, and that is we need to

hypothesis-drive these entry criteria to what it is we think we are doing. So we have designed a study, or at least the main criteria Peter suggested, were for people who had symptomatic diabetic polyneuropathy in which I am presuming that the outcome was to slow progression.

But we could design a study where nobody had neuropathy if we were hoping to prevent--if we had a drug that we thought, in people who had diabetes but who didn't have neuropathy, would prevent the development of neuropathy because this data, again, has already shown that there is a worsening.

So what I want us to be clear--and I do believe that there are lots of these little subsets, depending on how far down you want to drill subjects, you can drill them into large, small and motor-fiber function. You can drill them by quantitative sensory testing variabilities. But that doesn't matter until you decide what you think you can affect.

For the industry people, I think the problem is that there is no yet effective drug. One of the things that we talked about this morning in Eva's summary was part of that was inability to

predetermine, based on the expected outcome criteria, what might happen in the population.

So it would be important, again, if you thought you were going to do NGF again, you would want to enrich your population or pure your population. In people who had some small-fiber dysfunction, that was measurable at a site where you thought you could change it. That would be completely different when we looked at, for example, NT3 which, unfortunately, has died. But NTe is a large-fiber neurotrophic agent so you would want people where you had large fibers.

So they are all available. They are all in there but I think it needs to be hypothesis-driven based on your drug rather than this black box of, "We will do something with diabetic neuropathy."

DR. KATZ: I am going to try to go in order. Dr. Woolf, you were next.

DR. WOOLF: To me, there seems to be a confusion, at least in my mind, between the issue of a proof-of-concept trial where the entry criteria may have to be very tight to prove that the drug has an action and a second trial after that, where the generalizability could be tested.

I think the criteria of entry for those two kinds of trials may be very different.

DR. KATZ: Dr. Shafer, you were next.

DR. SHAFER: Actually, I appreciate Dr. Cornblath's going before me because this is really just following up on your comment, this particular commentary. I wonder if our taxonomy is correct in focusing so much on disease and not on mechanism of drug action.

Presumably, there is some mechanism by which the drug is acting which is why you think it might be effective. If we think the drug is acting in the periphery then, perhaps, the indication would be a demonstration of a peripheral disease which would be something like the nerve biopsy where you say, okay, we can see that there is degeneration of the small and myelinated nerves and that will be the population which we think will benefit.

On the other hand, if we think the drug is neuraxial in nature, then the entry criteria might be demonstration of a response to a neuraxial challenge as we talked about earlier. So, perhaps, a way of thinking about it is not to try to stratify patients by disease but rather what we

think is the mechanism by which the drug will work and demonstration that mechanism is likely to be effective in these patients.

DR. CORNBLATH: I think we are saying the same thing.

DR. KATZ: Dr. Feldman.

DR. FELDMAN: Really, I was just going to essentially say what Dr. Cornblath said that maybe, at this point, rather than talking about entry criteria if we talked about potential endpoints with some idea if we were talking about a small-fiber drug, a large-fiber drug or a drug that may be efficacious in both types of disease, we might be able to make some headway.

DR. KATZ: In lieu of making headway, let's do something else. Just to deal with the final issue that I think we need to deal with on entry criteria and then I promise we will go on to outcomes. I know it is very exciting for everybody.

Let's just talk, for a moment, about glucose control and how that should be dealt with at entry. That is a big question that comes up all the time. We have heard suggestions that symptoms may change in the context of increasingly tight

glucose control, that that can have an effect on nerve physiologic monitoring.

What level of glucose control is required has implications for the ultimate target population that we are trying to generalize to so I wonder if anyone has any comments about how to deal with issues of glucose control upon entry into such clinical trials.

Dr. Feldman, would you like to continue?

DR. FELDMAN: This is making headway. I can just tell you my experience in being a neurologist, not an endocrinologist, but from my endocrinology colleagues who are always involved in these trials, what they target for is stable metabolic control, as Dr. Dyke mentioned, and hemoglobin A1s in the range of 8 to 9 are frequently maximum.

I think some trials have even accepted hemoglobin A1s up to 10, but it would be unusual to be greater than that. That is usually used as the cutoff, hemoglobin A1, of course, in someone who meets the ADA criteria for diabetes. The stable metabolic control is, though, a very loose definition in my experience and it is kind of the endocrinologist's impression whether or not the

patient has been under stable metabolic control.

DR. KATZ: Is that the problem, that that is not tightly defined enough what stable metabolic control means?

DR. FELDMAN: When I was younger and more naive, I thought that when I entered all these Type 2 patients into my studies, into our studies, that, just because they would see us so frequently, they would enter and get really better controlled. But when these studies are long, which they are, a year, two years, three years, sometimes there is a small dip in control but usually they do have stable metabolic control. It is not that entering into a study--and that has really been our experience at the University of Michigan and I think that is a relatively global experience that sometimes there is a small effect. But, usually, how they were controlled is how they will go back to being controlled.

Dr. Dyke?

DR. DYKE: Can we ask Dr. Ed Bayster maybe to talk about this? We had a meeting recently with a series of diabetologists, and he is a diabetologist, where this issue was discussed at some length. Ed, are you here?

The issue from my point of view is, for John's sake, why don't we include these people with very high blood-sugar levels because they cannot, or they will not, get good control and they are the ones that need ancillary treatment. So, Ed, why are you making this fuss about metabolic control?

DR. KATZ: If you could just start with any relevant disclosures. Those are the rules.

DR. BAYSTER: I appreciate that. My name is Dr. Edward Bayster. I am a clinical research physician with Lilly Research Laboratories in Indiana as well as Clinical Associate Professor at Indiana University School of Medicine.

The issue has come up a number of times, as we have discussed trial design, on a number of different levels. The issue at stake or at hand is glucose control in the patient population which we would like to study. The patient population is a patient population with diabetic neuropathy and there are a number of epidemiologic studies that have been done over the years that have pointed out that this particular group of patients, on average, have hemoglobin A1C levels that are much higher than the population, the diabetic population, in general.

The question has always been is this the cause for their neuropathy or, alternatively, are they unable to obtain a better control because of the fact that they have high glucose levels. So that is the one side. On the other side, on the regulatory side and from an approach to a study and an ethical side in terms of taking care of these patients, we want them to have the absolute best control that they can during the course of a clinical trial or any kind of study.

With that in mind, the ideal patient would have diabetic neuropathy and perfect glucose control when they come into the study. However, because of the fact that that perfect glucose control, or that better glucose control, is oftentimes impossible in that patient population, what turns out or what is good enough.

So there are a number of strategies that one can then implement in an attempt to offer that patient the best glucose control during the study by offering all the metabolic glucose-lowering drugs that are available to do that, to lower glucose and to offer the best control. Then that patient, many times, is entered into the study.

One approach that has been population that

Julio Rosenstock actually published a very nice abstract on about a year and a half or two years ago at the American Diabetes Association suggested that, quite possibly, three months of metabolic control before the study for any patient with glucoses that were under 12 or 13--hemoglobin A1Cs under 12 or 13 percent, offered them the optimum chance for the best glucose control they can and that if, indeed, at the end of that period they had not gotten down to the magic 7 or 8 percent, that they were as good as they could be and that it would be ethical, then, to continue or to study that patient for diabetic neuropathy with the idea that we had ethically offered them the best metabolic control or the best care that we could with regard to their glucose control.

Many times, that included insulin therapy and in the implementation of insulin therapy. Certainly, for long-term clinical trials for polyneuropathy where adding insulin over the course of a three or four-year study can confound the outcomes. It offered the opportunity to actually start insulin in those patients in the three-month period to then take one more confounding factor out at the end of the day when you come forward with

your results.

So that is one possible approach to the problem. I hope that helps.

DR. KATZ: Thank you very much. I appreciate that. Any other comments about the issue of glucose control upon entry? Dr. Farrar?

DR. FARRAR: I think, at the end of the day, the question becomes why do we worry about their level of control. I think the answer to that is because it has been well-demonstrated that improving glucose control helps all of the potential side effects of diabetes and, therefore, what you need is a measure at the beginning and the end of your trial that will accomplish what Dr. Feldman was commenting on which is that there is a stable level of whatever measure it is over the course of the trial. That is what you are looking for.

I think there are a number of ways of doing that but, from a regulatory perspective, what would make sense to me is to ask that the measures of anything that would potentially influence the outcome of the trial be measured before and after to be able to assess whether it had an influence over what happened within the trial.

One last comment on it which is that, as somebody whose primary interest is in studying, actually, the clinical care of patients, meaning not the efficacy study which clearly needs to be done but looking more at the way in which patients are actually treated, you can do that. The issue with randomization is that you even out the two groups. If you add variance to your base population, you just need to expand the size of the group.

I think there are ways of handling it. What you need to be able to do from a regulatory perspective and from an interpretive perspective is to know what has happened to your patients over the course of that period. Whether the industry decides to have a three-month run-in or whether they decide to only use one particular group or whether they decide just to wing it and see what happens, if they have got the before-and-after measures that are responsive enough to see the difference, then, from a regulatory perspective, it should be fine.

DR. KATZ: Dr. Bril, you were next.

DR. BRIL: I guess my question to everybody would be since we know that, despite best

efforts, there are patients out there with poor control, and since they are the ones with the most frequent neuropathy and since, no matter how we know that improving their control will reduce complications, that the patient has to buy into it.

If they won't do it, is it truly ethical to leave them out of these research trials? We are ignoring them. We are saying, "You can't control your sugars, you can't come into this study." They are out there. They have the complications. This is not too ethical to me because they have gone through efforts to control their sugars.

They are on multiple oral hypoglycemics and insulin and they are still out there with the neuropathy or whatever it is. So the ethics to me seem to be that we are excluding them. So I would ask the agency for their comments on this. Could these people, if you have made efforts, come in and be randomized? This really bothers me.

DR. McCORMICK: There may be a number of different ways that you could deal with the patients who have particularly severe control. For one thing, randomization should take care of some of that.

The other thing that you might consider

doing is stratifying the group, looking at those with poor controls separately from those--or stratifying before you randomize so that you have the groups that are poorly control compared the well-controlled groups so that you could have a trial that would include all of those.

DR. BRIL: So there is no set level or number of A1C that they must hit?

DR. McCORMICK: No.

DR. BRIL: This is more industry-driven that it is--or is it FDA-driven?

DR. McCORMICK: This may have been FDA-driven at one point. I think this is something we have really done a lot of soul searching about for the same reason. I think our position has been more recently that we need to make certain that patients have the advantage of good--that, during the trial, they have best efforts made to insure good control so that they are not left to flounder during a very prolonged trial, but not to necessarily exclude them for poor control.

DR. KATZ: It sounds like many of these comments, at least tangentially or at least indirectly, endorse the proposal that we heard to give patients the opportunity to have the best

control possible during some sort of baseline stabilization period, then include them all and either stratify them or account for them some way in the analysis. I haven't heard any criticisms of that approach yet.

Dr. Feldman?

DR. FELDMAN: I just wanted to comment. One of the ideas I understood from our endocrinology colleagues is that when patients are in relatively good, loosely good, metabolic control, you are not going to be adding a lot of other medications. If they are under poor control, even if they are in a trial, then they are going to warrant other medications.

I can think of an example of three or four patients in the Zenarestat trial that we had whose control began to become relatively poor where their met forman was increased. Two of them bumped their creatinine. Was that from the Zenarestat which was discontinued because of high creatinine or was that from the met forman?

So my endocrinology colleagues have told me that one of the reasons we are doing this is because we don't really, truly understand the toxicity of these drugs. As we keep adding

different glucose-controlling agents to the drug we are studying, we may be getting interfering effects.

Again, the FDA would know much more than I.

DR. McCORMICK: Again, you do have a control group that you can use to sort out some of those adverse events.

DR. KATZ: Ms. Delph, you were next.

MS. DELPH: I think we need to differentiate between stability of control and level of control because it seems to me that stability of control talks about your trend, what is the trend of your hemoglobin A1C or whatever whereas the level of control says whether it is good, bad or whatever.

I think that, for individuals who have poor control, ethically, it would be important to ensure that every effort is made to improve that control but equally ethically, once every effort is made, they should not be excluded simply because of the level of their control.

If we are talking about stability as well, and, personally, I think that would be important, to look at the trend pre-intervention in terms of

glucose control but, also, I wonder whether it would not be important to look at the trend of the progression of the neuropathy before intervention.

DR. KATZ: Thank you.

Other comments?

DR. ARONSON: As I listen to the discussion, it strikes me that there are two perfectly laudable issues on the table. One is what can we do that is most fair to test the efficacy of the drug that we are wishing to test to begin with and wouldn't we allow ourselves the chance to do that best by only including those patients that are best controlled.

On the other hand, it is certainly true from an ethics standpoint that, by eliminating those other patients, perhaps the greater majority that are not likely to be tightly controlled, are we serving the best good in the best way. I think, again, it sort of comes back to what is our point.

Are we wishing to test the efficacy of these drugs and design a trial in order to do that and then should we go forward and see how we can serve the better good the greatest. I just with to have that point be made as well.

DR. KATZ: Dr. Cornblath.

DR. CORNBLATH: I think where a lot of this started in trials before was that there was this general association with poor control and more severe neuropathy. Where the more severe people were eliminated was because, on average, they had more severe neuropathy and it was thought they were less likely to respond to the agents.

So I don't think it was necessarily done because there was some level of inequality or discrimination but, again, it was hypothesis driven. It was driven by, "We don't think this is going to help them. Why should we put them in the trial," A, it won't help them and B, it will hurt the trial. So I think that is where the genesis of this was and we shouldn't forget that.

So I think there is good hypothesis reason for certain of the drugs to exclude these people because you don't really think you are going to make an effect. That, then, may have implications for what you say in your "label," but there were reasons to do it long ago.

DR. KATZ: Dr. Dyke?

DR. DYKE: It is clear from the epidemiology data that the risk factors for severity of disability sensory polyneuropathy are

other microvascular complications, notably indices of neuropathy. The second most important one is the average glycated hemoglobin control times the duration of diabetes. The third one is type of diabetes. So, in some ways, I have always argued that it would be an advantage to take the more severe neuropathies for the restrictions of ancillary treatments because this is really what we are talking about. We are talking ancillary in addition to glycemic control. We are talking about ancillary treatments.

So I would like it to be used for those more severe patients. There is a further reason. The people who have the more severe neuropathies tend to worsen to a greater extent over time than do the mild ones. So, from an industry point of view, you stand a better chance of showing an effect given that the drug works in those more severe ones because the changes are more rapid over time.

So I can see the diabetologist's point of view. The concern about not putting very severe diabetics into the study I think comes from the diabetes community. They feel it is sort of unethical, in a sense, if I can speak for them, to

ignore their blood-sugar control and stick them into a study, you know, this sort of idea.

So people want to cut it off at some level. I have always had the inclination that they should all be in there, especially those--that you should have a window of time when you encourage them to have good blood-sugar control. You might even have an algorithm of how you do that when they exceed the levels that you set.

But, at some point, you would allow them in. But I think it is coming from the diabetic community and, of course, one would have to defer to them for this decision about metabolic controls. So one lives with it. But if I had a preference, I would include some of those more severe ones in these studies.

DR. KATZ: Ms. Delph?

MS. DELPH: Thanks. My comments were just covered.

DR. KATZ: I am going to summarize this discussion and move on to the outcomes measurement issue. What I am hearing so far about the entry criteria are the following, and someone can tell me if I am getting it backwards.

First is that there is a need to decide a

priori what type of neuropathy you are trying to treat based on what you think your drug ought to be doing and then you need to select people whom you think will be responsive to that treatment.

Characterization of your neuropathy may depend upon excluding other types of diabetic neuropathy than distal-sensory polyneuropathy such as thoracic radiculopathy and cranial neuropathy et cetera. It also may involve the exclusion of nondiabetic neuropathies that may mimic diabetic sensory polyneuropathy like vitamin deficiencies, et cetera.

The diabetes, itself, needs to be diagnosed and the comment we have is that it should be ADA criteria. The diabetic neuropathy, itself, should be diagnosed by a composite measure which includes clinical as well as electrophysiologic criteria. What I seem to hear is that there is no specific standard about which composite diagnostic approach one should use. Someone correct me if I am wrong on that since it seems like there were a number of currently available approaches. So, correct me if that is not right.

Of course the severity of the neuropathy should be staged at baseline based on whatever

approach is chose. Lastly, glucose control upon entry or upon randomization should be stable and that stability is important but that tightness of control is not, by itself, necessarily required even though it could influence outcome and, therefore, should be accounted for either in a stratification or as a covariate or predictor of risk.

Did I miss anything big or get anything wrong? Dr. Cornblath?

DR. CORNBLATH: I would probably change the word when you say clinical features plus neurophysiology. I would probably change it to ancillary studies so that potentially skin biopsy could be included in that group so there would be quantitative sensory testing, nerve conductions of a variety of types, autonomic function, whatever there is in the term ancillary studies so that none of them are excluded.

Outcome Measures

DR. KATZ: Great. Outcome measures? What do we know about what constitutes an outcome measure that is meaningful to patients. We have touched on this in a lot of different ways before. Maybe someone could just boil it down into what

people think would be the optimal choice for outcome measure in a clinical trial. Would anybody like to tackle that?

Dr. Dyke?

DR. DYKE: I have thought a lot of about the issue of outcome measure in diabetic neuropathy especially for trials. I think there really are four major groups of outcomes, perhaps five. The first one is symptoms. The second one is impairments. The third one is test results which Dr. Cornblath just mentioned.

Then the fourth one would be tissue alterations. The fifth one might be other outcome measures of how well you are doing in work and leisure and general health measures. I think it depends on the trial that you are doing as to which you choose or the proportion or the ratio of the test which you use.

For example, the natural history of symptoms in diabetic neuropathy is quite different than the natural history of impairments. That needs to be taken into account in designing a trial.

We have noticed, and I mentioned it a little earlier, that not infrequently a patient

gets rather severe positive sensory symptoms; you know, prickling, asleep numbness, pain, lancinating pain or constricting pain, deep aching pain and so on. But, after a period of time, that goes away.

So if, for example, you focus on those symptoms and your goal is to modify those symptoms, you probably need a shorter study than you do for impairment. So, what kind of duration are you going to use for the clinical trial depends on what you are going to emphasize.

So a symptomatic trial I think should be relatively short because, obviously, you are going to pick the people who are, if you like, in a down phase. Then, by the natural history, people may get better on his own or he may fluctuate. So you are really better not to make that a four-year trial.

There now are some symptomatic trials which are positive for periods of a month, six months, and so on. For impairments, the Rochester diabetic study is absolutely rock solid that you need a long time. You simply don't get the power in a study unless you do it for about four years.

You can't overcome that by numbers. An insight came with the OCCT. I can't think of the

statistician's name. Vera? Eva? The man from George Washington--Kahill--the one who did the statistical--

DR. KATZ: It will come to you. Go on.

DR. DYKE: It is stopping my flow of thought, though, is the problem.

Dr. BRIL: Peter Lachin?

DR. DYKE: Yes. He told me that they didn't see an effect in the DCCT until four or five years and then the data came in like gangbusters. In the Rochester diabetic study we have shown that you see a large effect at about two years but you don't see it much before that.

So, in an impairment trial where you are trying to get separation of the treatment from the placebo group, you simply need time. It is a much more important variable than just the number of patients. So if you are using a composite score of clinical impairment plus nerve conduction plus sensation, I strongly recommend that you have at least a four-year trial.

On the other hand, if you do a complications trial, that is you are waiting for the foot to have a plantar ulcer or to have Charcot's joints, you are talking even a longer

time, at least data from the Sheffield group and our data would support that. So it really does depend what kind of a trial you are mounting and the endpoint.

DR. KATZ: We will have a specific discussion about duration of trials momentarily. That was a very useful introduction. I just want to make sure that we continue to--

DR. DYKE: Oh; you are not talking about duration here. I slipped a gear. Sorry.

DR. KATZ: No; it will come in handy in a moment.

Any other comments about outcome measures that are appropriate in these clinical trials?

DR. CORNBLATH: I mentioned this morning again, I think part of the difficulty in this issue is the fact that there is only--the biggest set of data comes from the Rochester group using the specific measures that they have pioneered and are quite good. It may be that, as I mentioned this NIH report, in other populations or with other measures, these time frames may, in fact, be shortened substantially. We don't know that.

So, for example, if, rather than looking at the great toe, we looked at the leading edge of

where pin sensation was and looked for a change of, let's argue, just for example, a centimeter to go one way, that may occur much quicker and you may be able to detect it quicker, but we just don't know that now. So there is a tremendous need for more natural-history studies in which many more of these outcome measures, or potential outcome measures, would be applied, particularly among other populations because when we admit a patient to a study in East Baltimore for a Mayo-designed study, it is not clear whether, in fact, the rates of change apply to the East Baltimore population. That is one of the several concerns I have about the fixation with four years or two years.

DR. KATZ: Dr. Feldman?

DR. FELDMAN: Really, just to reiterate what I said this morning, I do believe that a composite score, as a primary endpoint, is a very good idea. As Dr. Cornblath and Dr. Dyke said, a clinical component for that composite score that is quantitative, I do think, though, that it needs to be heavily based towards sensory impairment and not motor impairment and then couple that with two quantitative sensory tests, vibration for large fiber, cooling for more small-fiber modalities and

then, finally, couple that with some type of composite nerve-conduction score, the one that Dr. Dyke uses that has five nerves, the perineal, the tibial and the sural with those different components I discussed today, I think is very good, but a composite score.

I think that it is important that, at the end of the day, we probably concur or agree that there is not one single measure that would give us the home run but we really do need a composite score for our primary endpoint.

DR. KATZ: If I am not misunderstanding you, it sounds like you wouldn't necessarily choose the NIS as your first choice because if its heavy weighting towards proximal dysfunction and motor--

DR. FELDMAN: Peter, we were talking about that today in the NIS(LL). The component of it that I think is probably less helpful and it is really based on your own work are the Questions 17 through 24 that look at motor strength and the parts that are definitely more helpful are your questions, your two reflex questions and the four sensory questions.

So even a modified NIS(LL) or David has a very nice tool that actually looks at gradient

changes in sensation, so something that maybe would emphasize sensory more. I know your own work would support that.

DR. DYKE: I would agree. Where you do want the weakness score is when you get into more severe varieties because, as you go, for example, into the symptomatic 2As and Bs, you do get muscle weakness and you would want to record it. So if, for example, you focus on a more severe cohort, don't drop off the motor weakness, I would say. A mild one, an early one, I would agree.

Could I just speak also to the issue of quantitative sensory testing. A consensus statement has been prepared by a special committee of AAN on which I initially was a member and then dropped. It is going to be published, I understand. Just to reiterate, vibration is a very good measure and there are good algorithms now and fast algorithms and good quantitative approaches to look for the integrity of the alpha-beta sensory fibers.

Cool is a good measure of A-delta fibers. Heat pain is a very good measure of both hyperalgesia and hypoalgesia. Before patients get hypoalgesia, they get hyperalgesia. Just before

lunch, someone talked about that and it is a good marker of small-fiber disease and should be used. So we now have very good approaches for this, I would say.

DR. KATZ: It sounds like what I am hearing is that, at the moment, there is no validated composite-outcome measure that would meet everybody's needs since we are sort of deconstructing what has been done until this point. Is that a misunderstanding, or is there a state-of-the-art composite-outcome measure?

DR. DYKE: Could we restate that and just say that different composite measures might be used for different studies, for different outcomes. That would be fine.

DR. KATZ: Dr. Farrar, I am reading your mind and you are going to make a comment about the clinical meaningfulness of the composite-outcome questionnaires?

DR. FARRAR: No.

DR. KATZ: You're fired.

DR. FARRAR: That will come later. I can never resist talking about that. What I wanted to point out, and Dr. Dyke has actually addressed it, which is that the composite measure needs to meet

the needs of the trial. What I think is implicit in the NIS scale is an assumption that you begin with sensory abnormalities. When you get worse, you get motor abnormalities and that the two are somehow comparable, at least in some general magnitude way.

So if you have both sensory and motor, you are much worse than if you have just sensory. If you have a little sensory, you are not as bad as if you have a lot of sensory. I don't know that that is true, but that clearly is an assumption of that particular scale.

I think it is important to realize that composite scales are nothing more than a bunch of different questions that are added up. There are different ways of adding up the scale. You can add them up as simple numbers. You can multiple one times another. You can weight them differently. You can do what Dick Gracely did with some pain scales, measure them against something else and see who they work.

At the end of the day, the real question is what Dr. Dyke said which is what is the question that you are trying to answer in that trial. If you are studying a full range of people, which I am

in favor of, you need a measure that will be responsive to change in that full range.

If that is motor, then sensory, then reflexes or whatever it is, you need to be sure that that is properly included. One point; if you noticed when the scale was projected there--we couldn't read it, but just by viewing it--the number of questions that are asked in the composite scale defines the weighting.

If you put three questions about sensory and six about motor, you mean to say that motor is more important than sensory or it may be that motor is not as detectable as sensory and you need six in order to achieve the same amount of sensitivity as for the three sensory questions.

There is a whole science that has developed primarily around psychiatric measures looking at how scales--psychiatric measures and education measures. Actually, a lot of the best work has been done with the SAT scores--but looking at issue of how measures measure.

At the risk of suggesting that we don't reinvent the wheel, there are some very reasonable and straightforward processes that you go through to achieve an understanding of what your outcome

scale is measuring, especially for composites.

Some of the things I have mentioned here are fairly simple but there are also other ways of making the scale do the kinds of things you want. Just to mention one other method, something called the Womack, which is known to a number of you, is used to measure arthritis. The way that scale works is it is graded so that it asks about whether you can walk to the bathroom. It then asks if you can walk a block. It then asks if you can walk a mile. It says, can you go up and down stairs.

The whole purpose is that if you can only walk to the bathroom, you get one point. If you can walk a block and, obviously, walk to the bathroom--it is usually not clear that you can't do both--then you get two. If you can do that and then three blocks, you get three, et cetera.

So that is a different way to construct the scale. But I would suggest that, in terms of looking at these things, ultimately the issue is whether the scale measures what you want it to measure and whether it gives you the right weighting to the pieces that you want and that depends on what you are studying and how the scales are constructed.

DR. DYKE: Can I just agree with that? You know, we never conceived as the scale being sort of locked in cement and, for different purposes, we use different components.

But I do want to make the point that neuropathy is the sum-total of symptoms and disparate impairments and test abnormalities and outcomes. You need to be like an auto-body-shop man who goes with his yellow pad to the wreck of a car and writes down, "In this car, the headlight is missing. The front wheel is gone. The motor needs replacing," and adds it up. He ranks. Some score of some kind is needed.

In the eyes of fifty good men and women around the table, how you add that up or which components you think may vary and there may be better ways of doing it. But I think the fundamental idea is actually quite good.

If I could just go back to the early days of when the Social Security Administration set up the criteria for how you were disabled, they didn't want to just know, can you walk 50 feet and additionally go to the toilet and do you need a stick. They wanted to know has a scientist, a doctor, also examined them and showed that they

were also impaired.

That is what we have been trying to do is to give it that further evidence. I think it is very good to have life scales and what can you do, but Richard Hughes has a scale where, can you walk seven meters with a stick. Well, it depends on how big the nurse is that is helping you, et cetera.

I agree with them, but--well; enough said.

DR. KATZ: We are coming up on a break momentarily. Before we use up the remaining couple minutes of our time, I would just like to turn to the FDA folks and see if there are any further questions about polyneuropathy trials that you would like to hear addressed in the last couple of minutes of this session before we move on to pain after the break. Anything else?

DR. McCORMICK: I think we have covered all that we wanted to hear about.

DR. KATZ: Dr. Bril, you wanted to make a comment?

DR. BRIL: My only additional comment--I mean, the scales are just summaries of the symptoms and findings. You should use ancillary tests. As long as we are not locked into ancillary tests because they are going to change first, I think,

before the symptoms and signs depending on what they are.

The thing with quality-of-life instruments, if we select patients with milder neuropathy to go into these trials because they are the ones who are going to respond, they may or may not have a lot of impairment of quality of life. So, if you are going to look for change in an instrument, it would have to be impaired to begin with. There may need to be more thought about that, or you might have to stratify and subset people so that those who have impairments in quality of life can be measured for outcomes later of improvement or not.

But not everybody is going to have a bad quality of life, I think, at the beginning. So I have some concerns about that.

DR. KATZ: Ms. Delph and then Dr. Woolf, you will have the last comment. Go ahead, please.

DR. DELPH: I would like to urge that whatever endpoint is chosen that it be something that can be interpreted in a way that is meaningful in clinical practice so that adequate judgments can be made about whether or not it is going to be beneficial and how beneficial it is going to be to

a particular individual.

I also have a question about whether or not endpoints should be separated, for example, between sensory and motor-type functions or between the various types of nerves that are being studied.

DR. KATZ: Answers to that question? I think the composite outcome measures that are being proposed do separate out those different things and can be looked at individually.

DR. DELPH: But it was unclear if you are looking at one composite endpoint whether or not you are just lumping them altogether or whether you need to lump them together kind of separately

DR. KATZ: In other words, would the components of the composite-outcome measure be analyzed separately also as secondary outcome measures so you can gain insight as to whether the motor fibers or the sensory fibers or what have you are improving differentially.

Any comments on that? Is it traditional? Is it appropriate to separate out all the separate components or the main domains of the composite-outcome measure and look at them separately as secondary endpoints?

The answer is yes.

DR. CORNBLATH: Dr. Dyke and I were just talking. This has been done, for example, in the other CIDP trials where the whole NIS was used and then the weakness subset was looked at separately, and you can see dramatic changes in that.

So it is certainly possible to do from either a very large composite or even a smaller composite. It is just a question, again, of asking in advance what it is you want to ask.

MS. DELPH: And powering the trial to be able to interpret those.

DR. KATZ: Dr. McCormick? No? Dr. Woolf, last comment?

DR. WOOLF: Just a concern that, in the creation of these composites with all these weighting of these different elements, the assumption may be--it hasn't been stated but it often is implicit that these are linear scales whereas, in fact, they may not be, that in measuring them over periods of time, the sensitivity may be very different at the top end of the scale and at the bottom. So the significance of any change needs to be understood in the light that they may not be linear.

DR. KATZ: Yes. Validating these

composite outcome measures occupies professional psychometricians and statisticians full-time all around the globe. It is not an activity for people who don't do it on a professional level and we haven't certainly gotten into that discussion, and I don't think we will.

But, clearly, the professional nature of that activity needs to be kept in mind for those who would take a peril of inventing their own and seeing how it works.

Dr. McCormick, final comment?

DR. McCORMICK: No; actually one last question, if I might. One thing that we touched on a little bit this morning and some discussion about pain endpoints and effect sizes I would like the committee to think about in the context of neuropathy trials. Let's say we do finally have a drug that really demonstrates an effect, let's say, in arresting the course of disease or slowing the course of disease.

What kind of effect size would you think would be reasonable to see compared to a placebo? I guess we would be comparing the slopes of the two arms of the study, comparing the placebo slope, rate of decline, with the drug rate of decline.

What would be a reasonable effect size that you would accept that is clinically meaningful?

DR. KATZ: The first question, then, is which measure one would use and the second question is what change in that measure would be considered clinically relevant in a Phase III trial of a drug to slow down the progression of peripheral diabetic neuropathy.

So what measure and what change is clinically meaningful? Does anybody want to try to propose an answer to that question?

DR. DYKE: We talked about this at the St. Paul Peripheral Nerve Society four or five years ago. At that time, we thought that it ought to be at least two NIS lower-limb points. That is the delta. Now, that sounds like a very small amount but it is definable. It is the least amount of a neurological abnormality that a neurologist can recognize on two sides of the body.

But the epidemiology data actually shows that it is hard to get that kind of a result in trials because there is noise in all of these measurements. Time is involved. These patients are being treated with diabetes. But if you, in fact, saw this degree of difference at the end of

two years in otherwise well-designed trials which were truly double-blind, rigorously handled, if you saw that kind of data, most of us around that table at that time thought that that would be a meaningful change.

I should tell you, there were respected people including P.K. Thomas of London who thought we should just have statistical significance because it is sort hard to get significance in big trials with rough measures and lots of people involved and so on.

But we decided that and we needed, first of all, a really well-designed trial, large enough power to do the thing, double-blind and then we ought to have statistical significance, an NIS score of two points. The epidemiology data that we produced came later and it turned out it takes quite a large trial for a long period of time to get that effect on the assumption that the treatment arm of the trial is doing better than placebo.

So that was our answer at that time.

DR. KATZ: I am not sure that will necessarily get consensus on this question right now in terms of the best outcome measure and what

the best meaningful change is.

Are there other thoughts on that? Dr. Foster?

DR. FOSTER: It would seem to me, again from the standpoint of the progressive nature of this disease and your question about effect size, is that effect size is not going to be a single determination at X point in time after the start of the study. Instead, it will probably be a series of where you would look at both rate and extent of the change, would you not.

So it would seem to me that you would be designing the trial somewhat different than you would, for instance, an antibiotic trial in bacteremia, whether you do or you don't have bacteremia. Is that not true?

DR. KATZ: It seems to me that whatever outcome measure is chosen, it has to meet the one criterion of being ultimately linked to some sort of clinical benefit. From what I have heard today so far, myself--in fact, I took notes on this--there are three studies that I heard about that correlate change in some outcome measure with clinical benefit.

One was the increase in the vibratory

threshold which was correlated with foot ulcers. The second one was the Sosenko study mentioned that correlated changes in the thermal thresholds with clinical outcome, if I heard that correctly. And then there was the change in perineal nerve-conduction velocity which was correlated with clinically evident neuropathy. I am not sure if that really meets the criterion of clinical relevance or not since that sounded like a physician's evaluation.

What would people feel about using some of these quantitative measures, vibration threshold or changes in thermal threshold as outcome measures since there already seems to be a benchmark for clinical meaningfulness.

DR. BRIL: We had talked about this, and Peter just stepped out, I think, but if you are talking about slowing progression, what we had discussed at one time a few years ago was a 50 percent slowing of the rate of progression knowing that there is a more rapid progression in those with diabetic neuropathy compared to age-related changes in nerve function that are usual.

So if you could prevent the more rapid decline by at least 50 percent, there was some

consensus that that was going to be meaningful regardless of the magnitude of that change, but just that it was a 50 percent reduction.

You could look at VPT and see if you prevent people from getting to the 25-volt level that predicts foot ulceration but you would have to, then, know the rate of progression of VPT over the years and that is more problematic. So the prevention of progression in whatever scales may be the way to go, or one of the ways to go, rather than an absolute magnitude of effect which becomes a little problematic since you are not always sure what magnitude you are going to measure with time.

DR. KATZ: Dr. Feldman, last word for you.

DR. FELDMAN: Thank you. What we have done in the previous clinical trials, depending upon what the primary efficacy point or points were, since we know the rate of decline of these points from Dr. Dyke's work and from the DCCT and other epidemiological studies, what was actually aimed for was only a 20 percent change, a 20 percent change from placebo. That is how most of these studies were powered. That is how the zenerestat study was powered, for example.

Dr. Arezzo may be able to comment is that

is how the Zopolrestat study was powered. I think that is how the Alcar study was also powered. So a 20 percent change is what has been used previously.

Now, you are going to ask me whether that is clinically meaningful. You know, I simply don't know. I don't think we know if a 20 percent change is clinically meaningful but the thought was a 20 percent change in a short duration. These studies are mainly twelve months to two years.

DR. KATZ: A fifteen-minute break and we will return promptly to start the pain session.

[Break.]

Point-Counterpoint: Extrapolation of Findings from One Type of Neuropathy Pain to Another Neuropathy Pain Condition

DR. KATZ: We have a match coming up, the match of the century. There are bets being taken out in the hallway if anybody is interested.

We will start the late-afternoon part of our session on pain now. One of the major and most contentious issues as we have already gotten glimmers of today is whether one can extrapolate from efficacy in one type of neuropathic pain to other types of neuropathic pain and, if so, to what extent can on extrapolate and is there such a thing

as a drug that works for neuropathic pain in general.

So it was felt by the conference organizers that the best way to address that controversy is to have two of our resident experts take on the different perspectives in that controversy.

So, without further ado, Dr. Dworkin and Dr. Rowbothom, please share your thoughts on that topic.

DR. DWORKIN: The way we are going to do this is I am going to talk for ten minutes. Then Dr. Mike Rowbothom is going to do his prescription and rebut what I have said for twelve minutes, and I am going to have the right of first refusal to rebut what he said in another two minutes or, if all the wind is out of my sails, we will just open it up to questions. By the end of Mike's talk, all the wind might well be out of my sails.

I do want to emphasize at the outset that, in terms of the positions we are presenting, the position I am presenting and the position that Mike is presenting, these were assigned to us on the basis of a coin toss conducted by Dr. McCormick so you shouldn't necessarily think that what I am

about to say in the next ten minutes and what Mike is going to follow me and present in the next minutes after me is what we believe.

This is a true high-school-debate kind of format where we are debating what we were assigned to debate. So, without further ado--

[Slide.]

My presentation is a brief review of the evidence that supports separate neuropathy-pain indications. In thinking about how to present this evidence, the rationale for separate neuropathy-pain indications, it seems to me there are three types of evidence supporting separate indications.

One is that neuropathic-pain syndromes, neuropathy-pain conditions, I think some of you might refer to them as, have distinct patterns of symptoms and signs. The second is that they have unique combinations of underlying pathophysiologic mechanisms. And the third, and arguably the most important, is that there is specificity of treatment response already documented in the literature.

I am going to go through each of these in order.

[Slide.]

Starting with symptoms and signs, this is data that Dr. Brad Galer, who is in the audience, has published in two articles, in Neurology in '97, in Archives of PMNR in 1998, using the neuropathy pain scale that he and Mark Jensen published.

What I think you can see from this slide, and this is a bit of a glass half-full, glass half-empty. What I have done here is the plot the profile of responses in these five groups of patients, postherpetic neuralgia, complex regional-pain syndrome, Type 1, diabetic polyneuropathy, peripheral-nerve injury and Charcot-Marie tooth disease, plot the responses of the patients--these are averages--across these seven items or so on the neuropathy pain scale.

I have put an asterisk next to each of the items where there are significant differences among the groups. So you can see, what is it, four of the adjectives, that pain qualities differ among these groups--five, actually; sharp, cold, sensitive, itchy and surface pain distinguish these groups of patients. I think the conclusion of the story, and I quote Dr. Galer, is assuming that pain characteristics may reflect different underlying

pain pathophysiologic mechanisms, these data suggest the possibility that the mechanisms that produce postherpetic neuralgia pain may be different than those that produce pain in other neuropathy pain syndromes.

So there is a separation amongst these syndromes in their pattern, their profile, if you will, of symptoms, signs.

[Slide.]

Next, we all, I think, accept that the prevalence of mechanical allodynia is quite different in postherpetic neuralgia and painful diabetic neuropathy. For PHN, there are data. At least three studies have reported the prevalence of mechanical allodynia. This is almost always, although not always, brush-evoked pain. It is about 60 to 90 percent in PHN. I think we all agree that it is quite a bit less in painful diabetic neuropathy. I put down a guess of 20 to 30 percent. It might be lower than that.

A recent publication out of Israel, an open-label trial of lomotrigine concluded that the mechanical stimuli, paint-brush strokes, pin prick and repeated pin prick, evoked only minimal pain at the first visit indicating that mechanical

allodynia was negligible.

So not a lot of mechanical allodynia in painful diabetic neuropathy but very prevalent in PHN. So, the conclusion, with respect to symptoms and signs, is that they are different among neuropathic pain syndromes.

[Slide.]

Moving into mechanisms, Dr. Clifford Woolf who is here with us, published this illustration a number of years ago in The Lancet. I think there is little to disagree with in this overview diagram of the underlying etiologies of neuropathic pain, how those etiologies are a substrate of causes, really, of different neuropathy pain mechanisms that cause different kinds of symptoms, both stimulus-independent pain and stimulus-evoked pain, and then we have neuropathic syndromes.

I think one important thing that is not discussed in detail in this diagram is mechanisms. This is plural.

[Slide.]

We know from other publications of Dr. Woolf's that there are multiple neuropathic-pain mechanisms. So this is a figure from another recent article mechanisms of neuropathy pain and I

think nociceptive pain syndromes; ectopic discharges, central sensitization, sympathetic mechanisms. You are all familiar with this.

[Slide.]

So this is my revision of Dr. Woolf's figure. This I would propose is reality, that there are lots of different mechanisms. Notice, I used a ying-yang icon here to illustrate the fact that this is a debate.

These hypotheses, in this figure, are, as I tried to emphasize here, for illustrative purposes only. I don't want to spend any time at all discussing whether I am right in proposing that PHN, the mechanisms of PHN, are central sensitization and what else did I say, sprouting of A-beta fibers into the superficial dorsal horn.

The point of this figure, really, is to illustrate that I think we would all agree that we have got neuropathy pain syndromes, PHN, DPN phantom limb or breast pain, trigeminal neuralgia, idiopathic small-fiber sensory neuropathy and that there are a whole lot of different mechanisms that sort in different combinations with respect to determining the pain in those syndromes. In fact, if you look clearly at this fanciful illustration,

there are only two syndromes here where I propose, if you will, that the underlying mechanisms are identical and that is diabetic polyneuropathy and idiopathic small-fiber sensory neuropathy.

I don't know if that is true or not but, for illustrative purposes, if you believe that mechanism should guide treatment and you believe that something like this is reality, then the only two syndromes on here where you could actually make the extrapolation to treatment response in one implies efficacious treatment, in the other would be those syndromes, diabetic peripheral neuropathy and idiopathic small-fiber sensory neuropathy because the mechanisms of all these others are different combinations.

If anyone disagrees with that, I would love to hear the disagreement later on. So let's end up with differential patterns of treatment response.

[Slide.]

We all know that the results of placebo-controlled trials, as you can see going back to the 1960s, have established--and these are consistent with clinical experience, of course--have established carbamazepine as

first-line therapy for trigeminal neuralgia. But, as I say, at the bottom of the slide, no one thinks carbamazepine is first-line therapy for any other neuropathy pain syndrome.

Now, someone sent me a e-mail a week ago who is not even aware of this debate urging me to make the point at this meeting that trigeminal neuralgia shouldn't be considered in this discussion because it is just this peculiar idiosyncratic neuropathy pain syndrome and nothing that one would conclude about trigeminal neuralgia has any relevance to the other neuropathy pain syndromes.

So, even if we accept that argument, there is other evidence of differential treatment response.

[Slide.]

Here are two studies and authors of these studies are here with us this afternoon that concluded amitriptyline is not superior to placebo in painful HIV peripheral neuropathy. Of course, everyone in this room, I think, is aware that amitriptyline, for many, many years, has been considered first-line therapy in both diabetic painful peripheral neuropathy and PHN based on a

large number, at least 13 and maybe more, randomized controlled trials in those two neuropathic pain syndromes.

But here we have, if you will, replicate evidence of the lack of efficacy of amitriptyline in painful HIV neuropathy. Of course, one could quibble with these studies and maybe Dr. Max, who is an author on both of them, will quibble with the conclusion but, in fact, this study titrated patients to 100 milligrams of amitriptyline and this study titrated patients to 75 milligrams of amitriptyline and those are reasonable doses.

[Slide.]

Finally, and this is my last slide, two studies of dextromethorphan both of which conclude the same. One is about to be published in Anesthesiology sometime in the next month or two. Let me read these by way of conclusion. In the first study published in Neurology in 1997, out of Dr. Max's lab, the conclusion is, "In diabetic neuropathy, dextromethorphan decreased pain significantly relative to placebo. In PHN, dextromethorphan did not reduce pain significantly."

In the more recent study, dextromethorphan

is effective in a dose-related fashion in selected patients with painful diabetic neuropathy. This was not true of PHN suggesting a difference in pain mechanisms between the two conditions."

So I think very recent and quite compelling evidence that treatment response on one neuropathy-pain syndrome does not necessarily mean that there is going to be treatment response with that agent in another neuropathy-pain syndrome, even one, as we all thought, as closely associated with respect to treatment response as PHN and DPN. There is also a published study out of Dr. Max's laboratory showing lack of efficacy of dextromethorphan in facial neuralgias of various sorts. I just didn't have room for that on the slide.

So that is the end of my talk. The conclusion from these three sets of evidence that on distinct patterns of symptoms and signs, unique combinations, by and large, of underlying pathophysiologic mechanisms and evidence of differential treatment response, even when we wouldn't have expected it, dextromethorphan and amitriptyline in HIV sensory neuropathy I think suggests that one can't make the extrapolation from

treatment in one or two or maybe even three syndromes to treatment efficacy in neuropathy pain across the board.

Thank you. It is Dr. Rowbothom's turn.

DR. ROWBOTHOM: Now for the counterpoint. You would think that, with this debate, it would be natural for Bob to be the lumper and me, as neurologist, be the splitter and Bob, as a psychologist, be the lumper.

[Slide.]

After all, Bob, where you feel the pain is in the brain. But that is not the way it came out and, in fact, not only was I assigned the lumper, I was assigned to be the lumpier of the two. Although Dr. McCormick apologized for the typographical error in her message, I think it actually fits. No matter how much I grind away on this concept that neuropathic pain could be considered all the same from the treatment perspective, it is still going to be a rather lumpy pudding because there are differences between the different syndromes.

So let me just go through a few things.

[Slide.]

We have many different types of

neuropathic pain. They have different mechanisms. They have different clinical presentations. They have varying prevalences, varying diagnostic criteria, all of which makes study of them quite difficult. Most of the trials that have been performed for new drugs for neuropathic pain, the majority have been in diabetic neuropathy and then a smaller number have been in postherpetic neuralgia.

There are some syndromes where there is really even a question as to whether or not the pain is truly neuropathic. I had always considered CRPS Type 1 or RSD to be a neuropathy pain because the mechanisms seem to relate to abnormal function of the nervous system. But, even that concept, is being questioned now.

I was at a talk that Howard Fields gave last week at our pain-interest group meeting and he was saying that he didn't think it was a neuropathic pain really but an inflammatory disorder. So even all the old concepts are being revisited.

[Slide.]

The problems with spitting are--let's just look at it from a couple of different perspectives.

First of all, is there a distinctly different response to defined interventions based on diagnosis. I put there, "Just prove it," and I will go through a little bit of the data that Bob showed.

There is a lot of variability in the trials. We are so lacking in information to answer some of these questions that I think it is up to the scientific community and industry to try and really prove whether or not different syndromes are actually different from a treatment perspective or if there is a very broad overlap.

So, for example, I.V. lidocaine. Studies that we conducted many years ago and open-label studies prior to that have also suggested that neuropathic pain is much more likely to respond to intravenous lidocaine than other types of pain disorders, especially idiopathic pain or musculoskeletal pain.

My experience had been that patients with central pain were quite unlikely to respond to I.V. lidocaine. Then, sure enough, about a year ago, a very nice study by Nadine Natale working in France came out showing that patients with central pain did respond to I.V. lidocaine. So that point is

still up for grabs.

So there may be a difference between neuropathic pain and nonneuropathic pain for intravenous lidocaine but that, as a group, there doesn't seem to be any specific neuropathic pain syndrome that is particularly unlikely to respond to I.V. lidocaine.

Of course, some neuropathic pain disorders are extremely likely to respond to that. Patients with trigeminal neuralgia probably have an 80 to 90 percent chance of having their pain greatly diminished or even temporarily abolished with an intravenous lidocaine infusion.

Second, what about tricyclics and antidepressants. Tricyclics seem to be pretty broad-spectrum analgesics for neuropathic pain and probably the only type of neuropathic pain that they haven't been well studied in is trigeminal neuralgia. I would argue that, for the patient who is unoperated and, therefore, has a nonmanipulated trigeminal ganglion, the standard of care has been to treat them with a sodium channel-blocking type anticonvulsant like carbamazepine.

But, that said, tricyclic antidepressants are very potent sodium channel blockers. There is

every reason to believe that they probably would work in this disorder if they were to be tried. There really aren't good prospective negative trials showing that carbamazepine works and something like amitriptyline doesn't.

Just to underscore the potency of the tricyclics as sodium channel blockers, there was an interesting small study in the anesthesia literature where they actually showed that, in an animal model, you could produce peripheral nerve block by injecting a tricyclic antidepressant. It was that potent as a channel blocker.

The non-tricyclic antidepressants; is there reason to think that they would be unlikely to work in something like trigeminal neuralgia that is so sensitive to sodium channel blockers? Here, there is just no information at all.

There are really only a couple of non-tricyclic antidepressants that have much evidence of efficacy and these are all the mixed reuptake or the more adrenergic selective antidepressants with much less evidence for efficacy and, in fact, good evidence that they are not effective for pain with the serotonin-selective drugs.

So I think, from the antidepressant perspective, we either don't know or can't really make a strong case that there are disease-specific differences in response that are meaningful and important.

For opioids, again, trigeminal neuralgia being somewhat the exception because the pain is so typically phasic by the time you have got the medication into your system to try and treat an attack of tick, of the electrical jabs in the face that are characteristic of that, the attack would have ended. So that study has never really even been attempted.

For all the other types of neuropathic pain, to the extent that they have been studied, there isn't a clear distinction showing that one type of neuropathic pain is very responsive and all the other types of neuropathic pain are unresponsive. In fact, the problem is there is really just too little study and almost no published full-length papers on opioids for neuropathic pain.

Anticonvulsants; again, probably the best data is from the trials of gabapentin and pregabalin where, for the most part, all the

different neuropathic-pain disorders that have been studied have been found responsive to that particular pair of anticonvulsant drugs and, with the exception of carbamazepine for postherpetic neuralgia where it failed and more recently to piramate, which is a sodium channel blocker as well as having other effects for diabetic neuropathy, there hasn't been a lot of selectivity in that drug category, either.

Perhaps one could make a case that the topical medications, capsaicin and topical lidocaine, are selective for postherpetic neuralgia but that is probably, in part, at least, because they have not been studied systematically for disorders other than postherpetic neuralgia.

The next point I want to bring up is is there such a thing as a pure neuropathic-pain syndrome. The answer to that is yes and no. A patient with acute Zoster has neuropathic pain but they also have got tremendous inflammation along the peripheral nerve trunk, changes associated with inflammation all the way from the dorsal root and the dorsal horn of the spinal cord all the way out to the skin. So that is not a pure neuropathic pain. Only when they end up in a chronic phase,

six months or more after their original Zoster insult would they be considered more or less a pure neuropathic pain.

Patients with spinal cord injury, you could argue that that is pure neuropathic pain but, probably, really in the circumstance where they have something like an arterial-venous malformation that produces a spinal-cord stroke. But the majority of the patients that are going to be seen in practice are patients with traumatic spinal-cord injury and they may have associated spinal fracture, internal injuries or other kinds of tissue damage from the original injury that can give them multiple reasons for their neuropathic pain in addition to the spinal-cord injury.

Patients with multiple sclerosis may have many lesions. When we tried to do a study some years ago that included M.S. patients, I was surprised to see how many of them presented almost more like a fibromyalgia pattern. They hurt all over. They had definite multiple sclerosis. They met all the laboratory and imaging criteria for that disorder but their pains were not focal and associated with distinct abnormalities on neuralgia examination that one would typically associate with

central pain such as would be seen with thalamic stroke, for example.

Then, as Mitchell brought up a short time ago, what about back pain or neck pain with radiculopathy. The problem there is that relatively few patients have a pure radiculopathy without associated chronic neck pain or without associated chronic low-back pain.

I think that the people here from industry would probably agree that trying to study low-back pain with or without radiculopathy is almost the third rail of trying to do studies of agents primarily intended for neuropathic pain. It is a tough population to work with. Because of all the mechanical factors involved, then it is a difficult group.

I didn't put on this slide patients with CRPS or RSD which is another complicated group to work with. They are difficult to recruit and they often are quite unsuitable for clinical trials because their pain disorders are often tied up in litigation of one type or another.

The next point is what about the diagnostic certainty. Some of these disorders, one can make a quite confident diagnosis. A patient

with classic trigeminal neuralgia with, perhaps, imaging evidence of an aberrant artery and no underlying sensory deficit, that is a pretty firm diagnosis.

If you see a patient with acute Zoster and they continue to have pain, that is about as easy a diagnosis as you can get. But, for some of these other disorders, it can be fairly difficult to really establish that the pain is primarily or purely neuropathic and not due, in large part, to other problems.

Then, turning to what Bob was saying about the neuropathic-pain scale, the neuropathy pain scale, with the different mechanisms, and echoing a point that Clifford Woolf brought up earlier today that, because of the importance of CNS mechanisms, there is very broad overlap among all the different neuropathic-pain disorders so that there may be distinct patterns between the different neuropathic-pain disorders. This has been the focus of a lot of the work in our laboratory in San Francisco the last five or six years.

There still is quite a bit of overlap between the different disorders and there may be enough overlap that it would take very large

studies to try and really look at subtypes within the disorder or distinct pathophysiologic mechanisms to show that that had a very strong impact on study outcome.

[Slide.]

Turning to some of the more practical clinical-trial issues, I think, from the notes that I was sent by Dr. McCormick before the meeting, that we certainly want to encourage--there seems to be universal agreement on this point if nothing else, that there should be encouragement of studying a broad range of neuropathic-pain disorders, that many of the disorders that I listed in my earlier slide are disorders that are really quite rarely studied.

It has been difficult to convince people to study central pain prospectively. Some disorders are really quite uncommon such as adhesive arachnoiditis, a terrible pain problem when it occurs but it would be particularly difficult to do a clinical trial in a disorder that is that uncommon.

Also, some of the disorders are difficult to study from a clinical-trials perspective because the population that is afflicted has many other

concomitant medical problems. The average age of patients in postherpetic-neuralgia trials is 74.

When we enter patients with that disorder into some of our trials, it may take two pages to list all the concomitant medications they are on for all their other problems. I have always advocated for trying to have relatively broad and straightforward inclusion criteria to try and allow as many good research candidates into trials as possible.

In diabetic neuropathy, we have more or less given up on doing diabetic-neuropathy trials because anyone who comes to a pain-research center with diabetic neuropathy usually has pretty bad diabetic neuropathy and enough other diabetic complications or enough other sources of nerve injury that they often just can't meet entry criteria for a more typical industry-sponsored study.

Then, as I mentioned, particularly with back pain with radiculopathy, multiple sclerosis and, to some extent, postherpetic neuralgia, there may be a fair amount of inhomogeneity within the disorder, within the population that has the disorder.

Turning next to responsivity, there may be differences by disorder in the overall response rate. I would say that the one that is most likely to have a relatively low response rate would be the different kinds of central pain. Patients with spinal-cord injury and post-stroke pain are particularly difficult to treat.

The medical literature is littered with the debris of failed trials where they couldn't really show any change at all in pain. Diabetic neuropathies had, if anything, the opposite problem where the placebo response rate in some studies has been so high as to make it nearly impossible to show a differential effect with the active treatment.

In postherpetic neuralgia, perhaps the disorder is just the opposite. The placebo response rates in that disorder are quite low and my own personal opinion on that has been that, because there is such a high prevalence of allodynia that a patient, even if they thought they were doing better, all they have to do is touch their painful area and they very quickly get an index as to whether or not they are still in pain or not.

In fact, in some of our studies, allodynia, alone, is really quite a robust outcome measure.

[Slide.]

Let me just leave you with this for Bob's rebuttal is that perhaps there are a few special cases, postherpetic neuralgia because of the presence of allodynia, and the fact that it is a neuropathic disorder, it is a disease of the nerves, but there is such prominent involvement in the skin.

In trigeminal neuralgia, perhaps, because it is one of the only neuropathic pain disorders that is extremely responsive to surgery, to the point that surgery is essentially the first-line treatment once simple medication interventions have failed and where there does seem to be quite a fairly strong shift towards response to sodium channel-blocking agents.

So I will leave it to you, Bob, for your rebuttal.

DR. DWORKIN: I really don't have much of a rebuttal. I think we want to get this open for discussion as quickly as possible. I would just agree with Mike that I think, with respect to

patterns of symptoms and signs and of combinations of underlying mechanisms, there is, obviously, a kind of glass half-full, glass half-empty, issue.

But I think, in working on this presentation, the data that I have found most compelling with respect to splitting is these two negative trials of amitriptyline in HIV sensory neuropathy and the two negative trials of dextromethorphan in PHN in the context of two positive trials of dextromethorphan in diabetic neuropathy.

Those four trials, I think, are very, very difficult to consider from the perspective of the validity of lumping and having a broad neuropathic-pain indication.

But that is all I have to say and I think we should just throw it open for questions and then general debate. Mitchell, an author of all four of the trials, I am considering important in this debate.

DR. MAX: In the face of our four papers that you argued should be in favor of splitting, I am going to argue that the FDA and the panel should consider lumping in terms of a general neuropathic-pain claim.

As I said, I think the most important--the exception I will make to that is that we need to do something about nerve-root pain because you can't talk about neuropathic pain if you don't include that. But I think we have had a conversation in the past with Cynthia McCormick and Bob Rappaport and I think you have said we don't know enough now to know how to generalize.

I have got to say you are right. We don't. It is clear we don't know enough. My only argument for consideration of some kind of general neuropathic-pain claim is that, if it is true and this needs to be proven by some marketing data, if the goal of a general neuropathic claim would encourage industry to do more trials, that is the best way to answer your questions, to learn about it.

For example, the pregabalin program of studies I think has told us more about patterns of pain mechanisms than all the psychophysical studies we have ever done in that there are many trials that show gabapentin and pregabalin relieve diabetic neuropathy in postherpetic neuralgia and, in one trial, doesn't relieve osteoarthritis and it does not relieve the subset of people with

radicular pain.

So if a general claim would encourage more trials, we would learn from them. I suspect there may be a way you can do it fairly. So I would just like to put that possibility on the table.

DR. KATZ: Just a few points of order. First of all, thanks very much for doing a great job. I think you both can sit down because this conversation is going to go on for quite a while. So thanks for pitching in.

If people around the table could ask me before they call people up from the audience, that would be very helpful since there are some rules that we have to follow that I am hearing a lot about. So if you could just run that through me, please, although we certainly appreciate your comments and expertise, Mitchell.

Let's go ahead then and open up the conversation. The question at hand is does the evidence that we have available to us today support the extrapolation from success in one type of trial to success in another. It may be worth a word or two from the FDA folks to maybe remind the group on what the requirements are for the FDA to consider extrapolation in that context or to consider broad

labeling. Would that be all right?

DR. McCORMICK: I am not really sure there is any policy on this or basis or requirement, that is. I guess what we really need is--in order to make a general claim for neuropathic pain, that implies that we know that all of the various components are similar or respond similarly to a given drug.

So, while, in response to Mitchell's comment which is well taken, understanding that there is a need to stimulate research, I think that we are looking for a stronger scientific justification for making that cut, that there really is a basis for being able to link all of these together rather than generalizing to conditions that we really aren't sure are responsive to a given drug.

So while there is no policy, I think we need to have a good scientific basis for making our decisions and that is really what we are bringing to the table today.

DR. KATZ: Let me just take a moment and summarize what I heard to be your arguments and then we can bring it to the floor. I think it will help focus the discussion. So, Dr. Dworkin, I

think your points were that you feel that extrapolation, or you argue that extrapolation, is not appropriate because the symptoms can be quite different from one neuropathic pain state to another implying that the mechanisms must be different and, therefore, treatment responses must be different.

Dr. Rowbothom, I think I heard you say that, well, all is speculative, you really can't get a handle in most individual cases exactly what the mechanisms are. The fact is that, inhomogeneity, as you used the word, may be at least as great within neuropathic-pain syndrome as across neuropathic-pain syndrome. So that argument about mechanisms being different, preventing extrapolation may not hold any water.

I also, Dr. Dworkin, heard you summarize the literature that there is, in fact, a strong current within the literature supporting differences in treatment responses across different neuropathic pain states and the two examples you gave were amitriptyline for HIV neuropathy and dextromethorphan showing efficacy in diabetic neuropathy and not in PHN.

I think the question that you raised,

Mike, is that, are those the exceptions or are those the rules because we have these other cases which are, if anything, much more well-studied where we see gabapentin seems to have a relatively broad spectrum of activity. Pregabalin similar for neuropathic pain conditions in which it has been studied. Amitriptyline, yes; it doesn't work for HIV sensory neuropathy but seems to work for everything else that has been looked at systematically.

I.V. lidocaine. You mentioned opioids and there are other examples of where broad spectrum seems to be the characteristic of the different agents. So, are the points that you made the exception or are they the rule?

So those seem to be the arguments as I heard them. Maybe we could now open it up to see what people think about those arguments for or against extrapolation.

Mike, please?

DR. ASHBURN: I had a couple of remarks. I will have my back to Dr. Max so then I can take shots at him. Dr. Max used gabapentin as an example and actually pointed out a couple of the trials in general. I hope I don't misname them or

misdescribe some of the results of them but I actually want to use them as an example for not lumping. Gabapentin may be effective in postherpetic neuralgia. There is some data to show it might be effective in diabetic sensory polyneuropathy.

There is some debate with regard to its effectiveness for the treatment of the radicular component of low back pain. So what we think, what I think, you will see when individual agents are studied in different patient populations will most likely be a variable response to different indications since I think it is fairly clear that there are lots of different mechanisms and one medication is unlikely to be effective in a broad spectrum of different indications.

In addition, gabapentin has been implicated, if you will, in having other beneficial effects that are taken advantage by clinicians that may not necessarily lead to an indication of its effectiveness in neuropathic pain such as many physicians believe that it enhances the analgesic effects of potent opioids when used in combination with potent opioids.

It is also thought by the psychiatry world

to have anxiolytic effects which translate to analgesic effects in many patients who have mixed pain conditions. With that mixture, it is hard for me to conceptualize how one could combine all that and then get a general indication for neuropathic pain particularly since the end result is trying to prepare a package insert that guides a physician like me who does clinical practice on how to use that agent in these variable different populations.

How would that be written? How would I look at outcomes? How would I, on an individual patient faced with radicular low back pain make a clinical decision with regard to the risk versus the potential benefits? Gabapentin does have inherent risk. Although it is a fairly safe drug, there are significant dose-related side effects that one has to struggle with.

Many of the other agents that are used for neuropathic pain also share those. So I guess that it the point I am making is that, at this stage, a broad indication for neuropathic pain, while being a long-term objective might be very difficult to try to sort out because the different populations are so different.

Ultimately, it will be difficult, I think,

to be able to write an insert, or write indications to physicians, on how to use those medications in an effective way across broad different patient populations.

DR. KATZ: Other perspectives on this issue? Dr. Shafer?

DR. SHAFER: Earlier, we talked about different taxonomies and having a taxonomy organized by disease or a taxonomy organized by mechanism. Once again, we sort of endorsed the idea of taxonomy organized by mechanism but once again we are back to splitting based upon a disease taxonomy.

Since we keep coming back to this disease rather than the mechanism, my real question is are we just simply so ignorant about mechanisms and the fact that patients will come and they will say, "I have diabetes," but they won't say, "I have small-fiber disease," that we should abandon attempts to organize this discussion along mechanisms of neuropathy and just stay with the disease orientation or should we approach this, as we did with the other discussion, along the lines of mechanisms.

DR. KATZ: Dr. Woolf? Do you have

anything to say about mechanism-based approaches?

DR. WOOLF: I certainly heartily endorse that. I think the problem is that we don't have a full enough understanding of the mechanisms but, even more than that, we don't have the tools yet to identify in patients what those mechanisms are. Until we do, I think we are going to have to, in the real world, deal with package inserts to give instructions to clinicians.

But I think what it does raise is the issue that syndromes, and we discussed this morning for diabetic neuropathy, are not homogeneous so that Mike Rowbothom has shown very clearly, and I am surprised he didn't actually mention this in his talk, that postherpetic neuralgia is not a homogenous syndrome, that not every patient has tactile allodynia and he believes that you can identify different subgroups with different mechanisms which reasonably may respond differentially to different forms of therapy.

So I really think, and what I find really intriguing, is how much of the discussion this morning comes back--to talk about generalizability can only depend on the pharmacological activity of the particular drug. If it is going to potentially

act across many mechanisms, then that may be applicable. But, as we dissect out the mechanisms and the molecular elements, there are certainly going to be some drugs that are going to be very specific in their action and that are almost certainly not going to be generalizable.

So I think it is going to have to be done on a case-by-case basis. There are some drugs, like the opioids, which are not mechanism-specific. They act to operate on multiple sites in the neuraxis to modify sensory processing. They are not affecting the mechanism of the pain. They are producing an analgesia.

There are others such as sodium channel blockers that will only work on those situations where there is abnormal sodium channel expression or number. So I think it is inappropriate to say that, for all drugs, there may be an issue of generalizability, that they need to be based on what mechanisms are present, both in terms of the disease state and of the drug mechanism.

DR. KATZ: It sounds like what you are saying is that generalized activity needs to be proven for each medication.

DR. WOOLF: Right. I think there will be

drugs that are generalizable and I think there will be others that aren't.

DR. KATZ: If I could just push you a little bit further on that. Do you think that, at least in concept, there is a threshold that can be crossed by whatever package of trials necessary to get to the point where you can say, yes, this is effective for neuropathic pain in general?

DR. WOOLF: Yes. I am not going to define what that threshold is here. Maybe collectively we could, but I think it needs to be science driven in the same way that we now appreciate that Cox 2 inhibitors act by inhibiting Cox 2 and, if Cox 2 is not induced, they are not going to have any action.

I think we now are beginning to appreciate that the data is not really that strong, that the alpha 2 delta subunit of the calcium channel may be the target for the gabapentinoids and this is a subunit that is upregulated after nerve injury. If that is true across all forms of nerve injury, then one can make a scientific case why gabapentin and pregabalin may act in the broad spectrum.

But, as I said, there are other cases where it is quite reasonable to suppose that an alteration in vanaroid receptors may occur very

specifically in a subgroup of patients in which case the L1 antagonist will have a much more defined and smaller indication.

DR. KATZ: It sounds like what you are saying is that, in concept, one could conceive of a broad neuropathic pain-acting drug which ultimately, when we get to that point, could be determined scientifically through mechanism-based approaches but, in the meantime, since we don't have good mechanism-based approaches for people, it is possible that we could achieve that goal through other means which you have chosen not to define for the moment.

DR. WOOLF: No; I am not as defeatist as that. I think we are at a position now where, as we design our trials, we can attempt to define mechanisms as well. I think we need to use the conventional methodology with all its limitations but, in parallel with that, to try and get measures that at least reflect the mechanisms.

Bob showed his spaghetti junction of mechanisms. We need to try and see which of those are fantasy and which are reality. Certainly, we don't have all the measures to elaborate all of them.

Global pain scores, as we all use, as simple, whether as a categorical scale or Brad Galer's--those are so crude. We all accept that they are missing those elements of the pain that may be responsive to different forms of therapy. So we are lumping them together and maybe losing a lot of sensitivity.

So what I am arguing is that we need to collect as much data as possible, see how the different elements of the patient symptoms and signs respond the different treatments and try and identify that in the context of the different mechanisms that may be operating.

DR. KATZ: Dr. Bril?

DR. BRIL: I was disappointed in the results of tricyclics in the HIV population that we found because, if there was a lumping function, I could have seen it more with diffuse polyneuropathies that are painful, that are similar clinically, such as toxic or diabetic, because I think the pain mechanisms are not necessarily specific to the disease and I could have seen that.

But I have a little bit of difficulty with just a stamp saying neuropathic pain regardless of the etiology because what if you have a

carpal-tunnel patient. Shouldn't you be talking about splints and decompression rather than trying a medication right up for carpal tunnel? Maybe they need surgery.

So, if you were going to give a neuropathic pain indication, and this was in the inset, people may well misuse the medications for the indications you need. Something like postherpetic neuralgia or trigeminal neuralgia, which is treated basically with medications and, perhaps, surgery with trigeminal neuralgia really late, I can understand, again, lumping.

But just neuropathic pain of all kinds doesn't make much sense to me even with what we know now, and particularly the radicular question. I have a real problem trying to lump radiculopathies because there are so many other modes of therapy for radiculopathies. So that seems more problematic from a more basic point of view even than the molecular level at all.

DR. KATZ: Dr. Aronson?

DR. ARONSON: I was just going to reiterate so many of the comments that were made. I guess, as I hear this discussion, it is almost an artificial separation between lumping and

separating. I think there may, indeed, be, as we appreciate better mechanisms of action, commonalities across disease states and, if you will, differential within a disease state that we just simply don't appreciate.

The fear I have is that we will find a drug works for whatever that means and however we define it, but it is the right answer for all the wrong reasons because we just simply don't know what the reason is. So I think mechanism is so key to drive this discussion rather than creating these artificial silos of disease or mechanism or effectiveness.

I think we really must drive this by hypothesis in the beginning, what do we expect this drug to do and why do we expect to do it and test it in that sort of context.

DR. KATZ: Dr. Dworkin?

DR. DWORKIN: I want to argue a moment for lumping since everyone is arguing, it seems, for splitting. When I think about this issue, I can imagine an indication, being completely naive to the way the FDA thinks, that would be something like pain in peripheral-nerve injury and that would be supported, for example, by replicate trials in

diabetic peripheral neuropathy, a single positive trial in PHN, a single positive trial in HIV neuropathy and a single trial in paxil neuropathy that is positive, so a package of five trials across four conditions, all of which were positive.

If a company had that kind of package, I, personally, can't think of a strong argument why I wouldn't be comfortable with a lumped indication of pain from peripheral-nerve injury.

Clearly, we could come up with other conditions that are not on this list that I just came up with where the drug might not be efficacious but this seems to me like a large enough sample that I, personally, would be comfortable with lumping in that delimited way, pain from peripheral-nerve injury.

DR. KATZ: So you are saying that there might be the possibility to split neuropathic pain into largish subdivisions where lumping might be appropriate, peripheral being the example. One could also imagine central where you talk about stroke or what have you.

DR. DWORKIN: It is easier, in fact, for central because there are fewer syndromes so you can kind of capture, sample the universe of central

neuropathic-pain syndromes easier, I think.

DR. KATZ: So it sounds like, while it is not clear exactly what one would need to do the cross that threshold of being broadly efficacious for peripheral neuropathic pain, that there, at least conceptually, could be such a threshold.

Since you are a lumper now, let me push you a little bit further. Could you conceive of a threshold that could be crossed with central pain, the pain of spinal-cord injury, postherpetic neuralgia which is probably mixed central and peripheral, peripheral types of pain where one could actually become a real lumper and say neuropathic pain broadly.

DR. DWORKIN: I think, to follow the logic of what I just did, if you had replicate trials in one peripheral neuropathic-pain syndrome and replicate positive trials in central post-stroke pain, and the other peripheral syndromes I mentioned and a single positive trial in spinal-cord injury pain, a single positive trial in MS pain, how could that not be justification for a broad indication of neuropathic pain unmodified by either central or peripheral.

If the company had really sampled the

domain and, within the filing, had a couple of replicate trials, one peripheral, one central, I can't imagine an argument why that wouldn't be a broad indication.

DR. KATZ: Even though there might be some syndromes in which that very medication might not be efficacious and many patients within syndromes in whom that medication might not be efficacious which, as we know, is the rule.

DR. DWORKIN: There are always way-out exceptions. I think if you have sampled the universe adequately, you have to just tolerate that there might be an exception that shows up five years down the road in a negative trial.

DR. KATZ: Just to push you even a little bit further on that, would you then call amitriptyline a drug that is efficacious broadly for neuropathic pain given that the one exception, as far as we know, is HIV neuropathy?

DR. DWORKIN: I am troubled by the replicate negative trials in HIV neuropathy.

DR. KATZ: But given that that is the one syndrome that it seems not to be efficacious in, that would seem to fit with your scheme.

DR. DWORKIN: In fact, when you look at

the other literature, what we have with amitriptyline is a lot of positive trials in diabetic neuropathy, a lot of positive trials in PHN. There is a nice review of the literature by Sindrup and Yensen that everyone should have. If you look at that review, other than those trials in PHN and DPN, there is a single positive trial in post-mastectomy-pain syndrome and I think a single positive trial in spinal-cord-injury pain.

So, in terms of randomized controlled trials, it is not as good for amitriptyline as we all kind of think every day in the clinic. It is not the case that we have really sampled the spectrum with amitriptyline and found a lot of positive results. Amitriptyline and HIV neuropathy is an exception.

So I don't know about amitriptyline. It may not be as broadly an efficacious drug as we think. But I would be surprised that, if one did this program correctly with an opioid--I personally would be surprised if you didn't find efficacy across many of these syndromes that would support a broad indication.

DR. KATZ: Dr. Shafer?

DR. SHAFER: We seem to have general

agreement that if we knew mechanisms, that would be the right way to approach this. But we don't. We are forced into a certain amount of empiricism and there is this cross between virtually all the mechanisms in all of the states.

I wonder if the other means, to take a mechanistic approach, would be to actually define--to use response to therapy which is how we often look at mechanisms anyway, in which case a strategy, sort of borrowing from arms control, might be a lump-but-verify strategy where you say this is broadly approved, but we will verify, by therapeutic response in patients and then we will put it on the sponsors to say, "If patients are going to respond, they need to respond in three weeks, in four weeks. If they haven't responded, we are assuming that this drug is not addressing the mechanism appropriately."

DR. KATZ: Are you suggesting, then, broad labeling in anticipation of evidence of efficacy?

DR. SHAFER: No. What I am saying is that labeling would permit trying the drug out with specific instructions that, were it not to be effective in four weeks, that subsequent use would basically be off-label, that there would be a trial

period that would be part of the recommended therapy with the drug and it was to be discontinued if it did not reach--if it proved to be the wrong mechanism.

DR. KATZ: Ms. Delph, you were next.

MS. DELPH: A couple of questions and a comment. Are there a minimum number of disease states that you think a drug should be tested in or conditions that a drug should be tested in before you can lump it and give it a broad indication? Secondly, what about the use of animal models? Are there specific animal models that can be used to predict response even though patient populations may not be tested if you can't do all of them?

The final comment. To the best of my knowledge, HIV neuropathy, itself, is not a uniform disease. You have neuropathy secondary to HIV disease, itself, neuropathy secondary to toxicity from drugs like didanosine, stavudine and so on. So I have a question about HIV neuropathy as an entity in and of itself, whether that can be just looked at as one entity.

DR. KATZ: Dr. Rowbothom?

DR. ROWBOTHOM: I am glad you brought this point up because I was going to address some of

those anyway. I agree a lot with what Clifford says and that is that there probably are some drugs that really should get a broad neuropathic-pain labeling because they seem to work in so many different syndromes.

The issue has gotten a little more complicated in that a disorder that previously seemed to be pretty drug-responsive, painful diabetic neuropathy, was recently found to be unresponsive to topiramate which, pharmacologically, has enough similarities to other drugs that one would have expected that that would succeed in that disorder. So the equation has gotten a little bit more complicated because of that.

Turning to HIV and also the problem of central pain, if you set a criteria for a broad indication that said you have to show that it is effective in some list of four or five disorders, then that would raise the bar, perhaps, unacceptedly high because some pain disorders seem to be particularly difficult to treat.

Central pain, spinal-cord injury and post-stroke pain, very difficult pain syndromes to treat, and HIV neuropathy also appears to be pretty

stubborn, a pretty difficult disorder to treat. So we don't want to, or at least I wouldn't want to, suggest to the FDA--I wouldn't want to encourage the FDA to set their rules in such a way that there would be a strong incentive for the pharmaceutical industry to not study disorders like central pain and HIV neuropathy pain which are terrible, severe problems that really need more study because they are unlikely to respond.

Certainly, no one is going to want to study a disorder that never seems to get better with medications; right? That is pretty obvious as a bad idea economically. So what, perhaps, might be a way to go would be to try and encourage good studies in as many disorders as possible and, for the ones that are difficult to manage in the sense of being relatively unresponsive, to not necessarily require those be included for pivotal trials but that they be included as part of your safety data so that we do collect a large database on these less-well-studied disorders like HIV-neuropathy pain and central-pain disorders.

Hopefully, with uniform enough guidelines so that studies can be compared with each other so that gradually a large database can be accumulated

and we can start to answer the question of are some types of peripheral-nerve-injury pain particularly hard to treat. Are some areas of injury to the central nervous system--does an injury there confer a particularly bad prognosis as far as responsivity to treatment goes?

DR. KATZ: I want to make sure I understand what you are saying. It sounds like you are saying that you wouldn't want the FDA to require efficacy in all manner of diverse syndromes in order to get any indication at all but that studying them in syndromes with a track record should lead to those specific indications while, at the same time, you would like to see encouragement to study broad ranges of heterogeneous groups of neuropathic-pain patients not necessarily with the requirement of showing efficacy but more just to see if there is a signal there efficacywise and, also, to get safety data in these populations in whom the drug is likely to be used maybe off-label anyway, if I understood you correctly.

But I am still not sure what your perspective is on whether it is conceivable that drugs could have broad ranging efficacy and be labeled as such.

DR. ROWBOTHOM: I think that there are some drugs that should or can acquire a broad neuropathic-pain label. What that would mean is that their mechanism of action, where they work in the nervous system, is at a critically important place. Clifford mentioned the opioids, opioid receptors in so many different locations in the central nervous system, that really all the points involved in the pain transmission and modulation, there is some ability for opioids to influence the signalling there.

So that would certainly be a potential category for a broad indication. To the extent that we know it, drugs like gabapentin and possibly pregabalin seem to be moving in that direction. The tricyclic antidepressants, partly because they are such dirty drugs, they work on so many different transmitter systems that they also seem to be fairly broad-spectrum drugs for neuropathic pain.

So there certainly should be candidate compounds out there that could acquire this kind of labeling. My point was to say yes to that question but to also try and make sure that the criteria are set up so that we continue to acquire important

information, especially about safety and tolerability, in disorders that are less well-studied rather than continuing to study diabetic neuropathy and, to a much lesser extent, postherpetic neuralgia over and over again.

DR. KATZ: It sounds like you Bob have actually converged in your perspectives now. You have both become partial lumpers in the process of this discussion. But, if I could just push you a little bit further on some of these issues which is what I like to do, as you know.

You spoke about studies in heterogenous groups of neuropathic-pain patients as being useful because maybe they would identify efficacy signals that otherwise we would miss because nobody is going to do a trial on just patients with central dyskinesthesia syndrome from spinal-cord injury or whatever it is.

Would you see there being any role of Phase III clinical trials in patients with heterogeneous neuropathic-pain disorders which, although those trials may be very challenging to see any outcomes because of the heterogeneity of the patients, but if efficacy was shown, that that could be a more direct path to a broad

neuropathic-pain indication?

DR. ROWBOTHOM: If I understand you correctly, what you are talking about is a large trial where there were a spectrum of definable neuropathic-pain disorders that would qualify a potential subject for participation. So, for example, they could have multiple sclerosis and chronic pain related to that, focal peripheral-nerve injury, all these different disorders and then you would have a large study looking at the overall broad spectrum of neuropathic pain, or what we lump together as neuropathic pain, and then, within that, substudies that could, potentially, establish efficacy within the component disorders.

I think that makes sense. That is certainly a possible strategy.

DR. KATZ: Any other comments on that, on the scientific justification for that approach? John?

DR. FARRAR: Just a quick point. If you put together a group of neuropathic-pain patients and did a study, at the end of the day, I think what I heard Mike say is you would then have to look at the subgroups individually and show that,

in each subgroup, you had an effect as well.

DR. KATZ: I didn't hear that. Did you say that, Mike?

DR. ROWBOTHOM: I'll let him finish.

DR. FARRAR: Let me be specific, I guess. The point is that if you put together a heterogenous group and it was 50 percent diabetic neuropathy, 20 percent postherpetic neuralgia, a smattering of this and a smattering of that, and you showed that, on average, that group got better, I don't think that is evidence that it works in the other groups.

I think, ultimately, I end up being in the same camp as Clifford, and others here, in the sense that, without understanding the mechanism, I think it is impossible to be able to say that a drug works in everything.

I would like to make one other comment which is that Clifford also said, I think, that even if we know the mechanism, predicting that within an individual patient is going to be somewhat difficult and I think Dr. Shafer suggested a solution which is that we need to focus on not only whether it works in that group but then a study of why it works in particular subgroups

because, as we know, it doesn't work in everybody, like you said.

DR. KATZ: Just if I could understand you a little bit better. It sounds like what you are saying is that, if you had a trial of heterogeneous patients with neuropathic-pain, even though the mean response or number of responders, whichever outcome measure you like, was better in your treatment group than your placebo group, you wouldn't accept that as being broadly efficacious for neuropathic pain because it was driven by a subgroup of responders.

But if you had a trial of, say, something like gabapentin in painful diabetic neuropathy in which only 30 or 40 percent of the patients responded, driving the statistically significant response in your treatment group compared to your placebo, would you accept that as being indicative of efficacy in painful diabetic neuropathy?

DR. FARRAR: Absolutely. In fact, in the postherpetic neuralgia study, I would argue that it is not the mean value of the pain that was important. If you look at the paper that was published, 37 percent, approximately, depending on how you define it, of the patients who got

gabapentin got really better, meaning moderate or better, relief and only 15 in the placebo group.

Only a third of the patients got dramatic improvement. But you give it one patient who hasn't had improvement for ten years and they are suddenly better, it is good evidence.

The second issue there, though, I think somebody else had mentioned, is the issue of safety. If the drug has very few side effects, or serious side effects, anyway, you are much more inclined to be willing to try it in a person where there is a one-in-three chance of it working.

If the drug is like amitriptyline, I am going to be much less inclined to use it. I think that there are very significant side effects, especially in older populations, that worry me a great deal. So I think you have to make that tradeoff.

DR. KATZ: Again, just so I can fully understand, what is your scientific rationale for accepting success in a trial like the gabapentin trial when, in fact, the success is only driven by a subgroup of responders when you are not willing to accept success for heterogeneous, for broad neuropathic pain, when that success is also again

driven by a subgroup of responders.

DR. FARRAR: Because you can't predict looking at person with postherpetic neuralgia, at least not yet until Mike finishes his studies--we can't predict who is going to be responding. We can't divide the postherpetic-neuralgia group into groups where some of them respond, where there is a subsection of them that responded.

If we could do that, I would argue for trying it only in that subgroup. But, until we can do that, I think it is reasonable to try it in all again because it is safe. What you are suggesting is taking people that we actually think are somewhat different or have some differences that we can define, mixing them and then saying, because 30 percent of them respond that, somehow, everybody in that group is the same.

I think there is a very distinct difference. In the postherpetic-neuralgic group, we cannot identify, a priori, the differences. Now, Mike has started doing some research that hopefully will move us toward being able to do that. But, until that happens, I don't think we can do it.

DR. KATZ: Any regulatory perspectives on

this issue of studying heterogeneous groups of neuropathic-pain patients?

DR. McCORMICK: I think that we are answering the question that we are all struggling with with an example. I think that to embark in a study that has a heterogeneous group is making the assumption that we already know that lumping makes sense. So I think that first we need to answer the question does lumping make sense before we encourage trials in heterogeneous groups.

DR. DWORKIN: Stating the obvious, I think we have all seen data with heterogeneous groups of patients where the significant efficacy is based on a subgroup of not responders but a subgroup based on diagnosis which suggests you shouldn't be lumping, if the overall significant difference comes from a subgroup of one diagnosis.

DR. KATZ: Does anyone else have any final comments on the lumping versus splitting issue? Dr. Woolf?

DR. WOOLF: Just to address the second part of Ms. Delph's question about animal models which got lost somewhere along the line. I think that is a very important issue and I think animal models need to be looked at as critically as we are

looking at the clinical development of programs.

There are many problems there. The problems are that the animal models have been designed to reliably produce symptoms that are "pain related." Some of them are designed to be models of disease. Very few are designed to be models of mechanisms which is what we are aspiring to. Again, we don't often know what mechanisms operate in those models.

More significant is the problem that all we can measure in animal models are responses to stimuli. We cannot measure spontaneous pain which, in diabetic neuropathy, is the biggest problem. So we use outcome measures which are convenient but may often be irrelevant such as heat. Hyperalgesia is the commonest outcome measure in animal models but is not a problem that any patient ever complains of.

I think one of the most significant issues about predictors is that we can use doses in animals where humans wouldn't tolerate. It is very difficult to measure side effects such as dizziness or sedation. So we can get effects in animal models that we would never be able to escalate a dose in a patient to get the equivalent effect.

So I think animal models are essential. They are going to, obviously, always drive the drug-development program but they are never going to be a surrogate for human trials, in my opinion.

DR. KATZ: Dr. Rowbothom?

DR. ROWBOTHOM: One thing that I think is, perhaps, a little separate from the regulatory issues and that is that, as these trials are done, we want to look at the group that is responding and the group that is not responding to see what we can learn from a clinical-mechanisms perspective as to why those patients diverged into responders versus nonresponders.

The other aspect, the regulatory aspect, is that there is a model for what we are talking about, large studies of mixed neuropathic pain in the form of the pregabalin studies that have been done where the study designs are relatively similar. It is a series of studies in different diagnostic groups.

Their approach was to study some neuropathic pain and then include some disorders that are thought to be nonneuropathic like fibromyalgia and osteoarthritis. The value in that data, of course, as John Farrar knows really well,

is that it is a gold mine of information about how patients respond in general and pain characteristics and all these other things.

But that is an approach that has already been taken that is similar to what we were talking about before where if you look at a variety of chronic pain disorders including ones that are known to be pretty treatable as well as ones that are believed to be relatively refractory to treatment, that is a valid approach as long as you make sure that the number of subjects studied with each diagnosis is enough that you have an adequately powered look at that particular diagnosis.

DR. KATZ: Any final comments about the lumping versus splitting issue before we move on? Dr. McLesky?

DR. McLESKY: Dr. Hertz actually raised this issue I thought in response to a comment real early today when she was asked the question would it make sense to do two pivotal trials that are very similar or would it make sense to do potentially two separate trials that might corroborate one another in potentially somewhat different populations?

Speaking for industry, I think we would like to have feedback. Maybe you could elaborate on that just a little bit more, if you would. Also, I would like feedback from the panel. If we were going to lump, if it did make sense to lump for a particular drug, how many different kinds of patient populations would it make sense to test in order to be able to logically lump?

DR. KATZ: Boy, I don't know that we are going to get that today. Does anyone want to throw any proposals or comments? Sharon?

DR. HERTZ: The comment I made about replicating studies was not replicating different diagnostic populations but, within diabetic neuropathies, not to mimic the exact study design at the same center or group of centers but maybe to take two meaningful study designs in the diabetic population across centers and then have a slightly different approach just to show that this wasn't just one very, very large study which has a whole separate discussion.

So it really wasn't referable to different diagnoses.

DR. KATZ: So it sounds like what you were saying, Dr. Rowbothom, was that repeating very

similar studies in different diagnostic populations is very useful for characterizing the spectrum of the drug where as Dr. Hertz is saying that, to really prove the point about any individual indication, two trials that support each other but may not be completely identical could be an optimal approach.

Bob?

DR. DWORKIN: What I had said earlier, and I guess I would stand by it, for peripheral-nerve-injury pain, I think four or five different conditions for me kind of is enough of a sample of the universe and, for central pain, three because I just can't--beyond a certain point of those numbers, there are not that many syndromes left.

DR. KATZ: Dr. Woolf?

DR. WOOLF: To maybe expand the lumping and splitting debate, as you are about to close it, we haven't split in terms of different elements of the pain so that if, for example, a drug could be shown to act only on spontaneous pain and leave evoked pain unaffected, or the opposite, tactile allodynia was sensitive, and tactile allodynia was expressed across a different range of patients both

peripheral and central, what are the implications of that in terms of either trial design or potential label?

Patient Populations

DR. KATZ: I am going to use that actually as a segue to move on to the next topic which is related to your question which is how should we characterize our patients upon entry into a neuropathic-pain trial, what tests should be do, what examination procedures, how can we define what population we are dealing with.

It seems like everybody agrees that we should all be working towards trying to understand better what patient characteristics might confer a responder status upon that patient eventually maybe towards a mechanism-based approach to treating these illnesses. So what do people think about how we should be characterizing our patient population upon entry?

DR. BRIL: I will start off. In the specific case of diabetic neuropathy, I think we need to establish the severity. I know I have been involved in some trials in which the diagnosis was assumed and very little independent objective measure was done other than symptoms and signs, and

those patients--this was a study of just pain.

But I think the studies are strengthened by the information on better responsiveness in those who have, say, a sural potential present meaning that staging of severity might improve the trials and improve our understanding and the outcomes.

So I think I would make a recommendation or a suggestion that pain trials in diabetic neuropathy be not considered simply studies of reducing pain but look at the severity and relate it to the outcome.

DR. KATZ: How would you do that, specifically?

DR. BRIL: Specifically, at this point, by doing sural-nerve conductions and splitting into sural-nerve positive or sural-nerve absent. I think the QST, the vibration-perception thresholds are a little less understood at this point. We haven't divided them and looked at outcomes so well so that I would look on severity as stage by sural-nerve responsiveness.

DR. KATZ: Just to state the obvious, duration of disease, severity of pain, all those things, neurological exam, all those things. I

don't think we will find any disagreement about the need to include those.

Dr. Farrar first, then Dr. Shafer.

DR. FARRAR: I think that we are limited to a degree by what we know and that was said to a great extent in our earlier discussion. I am very much in favor of taking a group of patients, let's say, who have postherpetic neuralgia and including them all in a study in which we then measure, I guess, the equivalent of a sural-nerve conduction perhaps looking at allodynia and nonallodynia, measuring the number limited by, obviously, patients' tolerance for testing but measuring a number of different features that we think might actually help to differentiate subgroups within that overall disease category and then looking post hoc at that, not looking for the answer but looking for the hypothesis for the next study.

By that mechanism, we can both study compounds that may be useful as well as get some sense about the underlying mechanisms.

DR. KATZ: So you are advocating characterizing patients upon entry based on their sensory abnormalities, basically?

DR. FARRAR: Yes. Certainly, that is one

of the components but it may also be that duration of disease is important. It may also be that the location of the process, whether they were treated aggressively early on or not, their age, et cetera. There are obviously many features and you would ultimately design or look at an etiologic model and a predictive model afterwards to try and generate hypotheses for which groups respond and which ones don't.

DR. KATZ: Dr. Rowbothom, do you have any comments on the appropriate of trying to characterize patients in PHN trials based on sensory abnormalities or other criteria?

DR. ROWBOTHOM: The easiest one is to characterize them in terms of the severity and spacial extent of allodynia. We use a foam paint brush which is inexpensive and it is quite reproducible. It is something that is suitable for multicenter trials because it is quite easy to train somebody how to do that in a reproducible manner.

Some of the more specialized techniques that we have used, like capsaicin response and skin biopsy is much more difficult or just much harder on the patients. The capsaicin can be quite

painful for them so that is not something I would really advocate applying large-scale across all different kinds of compounds.

But, certainly, for that disorder, allodynia should--I would very strongly advocate that be followed.

DR. KATZ: Brush allodynia? Anything else?

DR. ROWBOTHOM: I think that you get into a complexity problem when you start trying to go multicenter. We were involved in one small study where there were four centers and we did very, very detailed quantitative sensory testing and sensory mapping. Although we were able to come up with pretty good agreement in the measures, it was an enormous amount of work to do that, and that was four university-based centers that had all previously published in that area beforehand.

So, if you start trying to go from there into the more typical multicenter study where are maybe ten or fifteen or twenty centers and you start going more into community-based practices, then I think that level of sophistication starts getting really difficult for a disorder like postherpetic neuralgia.

DR. KATZ: Dr. Shafer?

DR. SHAFER: I think I am just stating the obvious, but you had asked earlier about different kinds of pain, spontaneous pain, for example, versus evoked pain. I would say that if a company doesn't know if their drug is better for spontaneous pain versus evoked pain, they are not ready to enter a pivotal Phase III trial where they select one or the other.

There need to be some Phase II trials to figure out what it is they think their drug does before they then get around to actually designing that Phase III trial and moving forward with it.

DR. WOOLF: I think if you look at almost every published trial, you won't find that data available. These are global scores. There is no way of identifying whether it affects--most patients are never tested to see if they have stimulus-evoked pain.

DR. KATZ: When it has been examined, when it has been looked for, how different subtypes of pain respond to different medications, can anyone summarize the results of that for us, trials where people have tried to segregate different types of neuropathic pain and see whether there is a

differential treatment response.

DR. BRIL: I remember from reading in the amitriptyline studies that the stabbing pain would respond to it. So would burning pain. It is difficult because some of the different types of pain respond to the same agents. They are not all yes or no, respond or no respond, depending on pain, plus the patients are not all stimulus-evoked pain or spontaneous pain. They tend to have a mixture of pains and that is why you don't see it in the studies because they change all the time.

So I am not saying it not easy to drag out, but what I have seen is--well, in the clinic, the patients don't split into categories and, two, I remember the amitriptyline story on those pains and carbamazepine was better for stabbing pain, I think, and not as good for burning. But I don't remember all the details beyond that.

DR. DWORKIN: Certainly this notion that persists in the literature that the tricyclics are good for kind of steady burning pain and anticonvulsants are good for intermittent paroxysmal pain. But, in fact, if you look at the studies that have assessed different kinds of pain, the tricyclic studies that Mitchell has done and

Soren Sindrup have found responsive of intermittent pain, ongoing pain and allodynia for tricyclics.

Peter Watson has found the same thing in the OxiContin study in PHN. The gabapentin studies haven't really looked at stimulus-evoked pain but unpublished analyses of the McGill short form show a responsiveness to gabapentin irrespective of type of pain.

So, in fact, the data we have suggests that these three types of agents, if they work for one type of pain, are very likely to work for other types of pain and so there isn't a symptom specificity.

DR. KATZ: So I think we would all agree, somebody correct me if I am wrong, that assessing the different subtypes of neuropathic pain is important as we attempt to learn more and more about this phenomenon and work towards a mechanism-based approach but not to have high hopes because so far it hasn't panned out.

Is that a fair summary?

DR. ROWBOTHOM: I am not sure that I agree that it hasn't panned out. Part of the reason why I was not strongly advocating things like skin biopsy and capsaicin response is just that they are

not easy to do. They are not easy to get analyzed. I think we need a little more data from more the level of single-center or small multicenter studies before you start trying to incorporate that into a set of guidelines that would apply to industry as a whole.

So that was really more my caution, not that they hadn't worked out. It is that there just really wasn't really enough known yet to really push strongly on them.

DR. KATZ: Fair enough.

Dr. Farrar, you were next.

DR. FARRAR: I would like to just address two issues to you and let you decide as to how you want to approach them, but there are two other issues that need to be addressed with regards to pain specifically. One is whether patients who have successfully been treated with another agent, either similar or not similar, need to come off that agent before they are tried.

The second is whether or not multiple therapeutic options are allowed the patient. In specific, this comes up with cancer patients all the time is that it would be unethical to take them off of their opioids to study gabapentin. What we

would do is to do an add-on trial, as is often done with epilepsy drugs. Those are two areas that we haven't covered.

DR. KATZ: Right. That is a great point. That is actually on my list of miscellaneous things to get to if we have time, and I hope that we do. So let's hold that question for a second.

Are there any other comments about characterization of patients on entry. It sounds like we have advocacy for doing neurophysiologic studies for diabetic-neuropathy studies and presumably other polyneuropathies, at least assessing allodynia in such patients, characterizing symptoms based on the specific type and all the other things that I think are obvious.

Any other points about characterizing patient populations? Dr. Feldman?

DR. FELDMAN: Just a point that I know Vera is well aware of but certainly nerve-conduction studies as we have discussed primarily are good for large-fiber modalities and most of the pain that we are discussing today are small-fiber modalities.

Vera, I had to step out for a moment, but you are saying you want to use nerve-conduction

studies just to get an idea of the severity of the generalized neuropathy?

DR. BRIL: Yes. In some previous studies, the responsiveness to pain was in those who had sural-nerve responses present. So it is staging severity. It is just staging as you enter. I mean, there is a role to look for neurotoxicity if you thought you were going to get a toxic effect. So, for safety, you might do it. But, basically, at the beginning for staging to try and subdivide the patients.

Primary Endpoints

DR. KATZ: What should be the primary endpoint in neuropathic pain in clinical trials?

DR. BRIL: Reduction of pain.

DR. KATZ: Thank you. Anybody disagree?

DR. RENDELL: That, of course, seems to be reasonable but one of the questions I have always had is why do we only do such short-term pain studies? They are always twelve weeks. The answer to that is that is what the agency wants. But, is that reasonable? The reason I am asking whether that is reasonable is because in the diabetic-neuropathy area we are now using pain studies as a surrogate for studies of actual

diabetic neuropathy realizing we can't find any drugs that will ever treat or meet the criteria for approval of diabetic-neuropathy drugs. Why are we only going twelve weeks? Why don't we go a year? Why don't we go two years?

DR. KATZ: You are referring to placebo-controlled trials that last that long, monotherapy?

DR. RENDELL: The studies we are now doing are very short-term. They require that patients go off all their other pain drugs but the problem is companies are simply substituting pain studies for diabetic-neuropathy studies. They are doing that intentionally with the hope of getting approval.

DR. KATZ: Anyone have any thoughts on that?

DR. BRIL: Can I ask--the reason that I see that patients have to come off their other drugs and the reason I have always thought that was a good idea for pain and painful neuropathy was that there seems to be that refractory core of patients who have painful neuropathy.

If you start recruiting these patients into studies, you may be biasing yourself to a failed study whereas if you have patients who are

not on multiple drugs, you stand a better chance of showing efficacy. That is what I think. But maybe that is just a wrong opinion and maybe an add-on to somebody who is on two or three other drugs, and add-on study, would still have the potential of showing an effect.

DR. RENDELL: Do we want patients with such severe pain, at least in those studies that are surrogates for diabetic-neuropathy studies?

DR. KATZ: I am interested in that point about studies on pain being used as surrogates for disease on occasion--I was not aware of that.

DR. RENDELL: What is happening the companies are admitting that they cannot get a drug approved for diabetic neuropathy. What they are doing is they are using pain as a surrogate at this point.

DR. KATZ: Anyone have any knowledge about that?

DR. RENDELL: Vera certainly does?

DR. BRIL: No. I don't think I agree that that is what happening. I do see that there are medications being developed strictly for pain or that are out there already, gabapentin being one, and that is being studied more now for control of

painful symptoms and different agents.

I know of novel antidepressants and novel anticonvulsants that are being studied strictly for the control of painful symptoms. I do know of some agents that are being tested to reverse or interfere with disease progression, to halt or slow down or reverse disease progression and that these agents are being studied from multiple points the way we discussed earlier so that they are being assessed with respect to their effect on neurological deficits on examination and on ancillary measures such as nerve conductions and quantitative sensory thresholds.

Some are being studied by the Peter Dyke scale composite score. They are also being looked at with respect to their effect on symptoms which is what I think we all want. I mean, it would be wonderful to have a specific agent that reduced neuropathic symptoms and improved nerve function and reduced the sensory loss on exam.

If you had an agent that did all of that, it would be a tremendous advance in the field because we have nothing that does that.

DR. RENDELL: But is twelve weeks enough?

DR. BRIL: But these studies that I am

talking about are not just twelve weeks. The twelve-week studies are basically the ones that are designed just to show an analgesic effect for the painful symptoms the same as they are in postherpetic neuralgia or whatever other pain thing you want.

I think that the issue is a little bit the placebo-control group. It is difficult to go beyond twelve weeks. But perhaps you need longer studies to see if the pain really is sustained. I mean, that is not a bad idea.

DR. RENDELL: That is one of the questions. Isn't one of the endpoints how long the pain is relieved and what happens after the pain is relieved.

DR. KATZ: Dr. McCormick?

DR. McCORMICK: I hear two questions. One is the question of why are trials that are designed to look at symptomatic relief of pain only three months long? Is that the agency's standard and why is that?

I think that we have considered three months for most conditions an adequate length of time to determine that a drug is either working or not working for symptomatic relief of pain. Now,

that may not be correct and I would like to hear further discussion on that point as to why longer trials might be needed.

As to the other point of the twelve-week trials in pain being used as a surrogate for disease progression, that has not been our experience. Clearly, trials that are intended to look at the progression of disease are far longer than that and all sponsors that have come to us to date have come to us with that realization and with that expectation that they are in trials for the long haul, that these are going to be very long trials.

So I don't think there is a single sponsor yet that has come to us. Now maybe these trials that you are thinking of are still in the conceptual phase but, for the most part, sponsors that have come to us have not had the perception that a three-month trial would suffice for an alteration-of-disease claim.

DR. KATZ: Ms. Delph, you were next.

MS. DELPH: I would like to add in the discussion of safety when we are talking about duration of trials because I would like to hear what people think would be an adequate duration for

pivotal trials especially looking at safety and, secondly, postmarketing studies. I don't know if you are going into the postmarketing period but certainly, in HIV where we have a lot of fast-track approval of drugs, one of the big, big, big problems we have had is postmarketing safety studies.

DR. RENDELL: In what respect?

MS. DELPH: Getting companies to do them.

DR. KATZ: Let's focus on the duration of trial issue and then we can talk about safety monitoring as well. Does anybody else feel that three months is not an adequate length for a trial and you can be specific about what can be accomplished by longer trials.

Dr. Farrar?

DR. FARRAR: I think it is important to keep in mind that the two different lengths of trial are going to answer different questions, both of which are valid. I think it is up to the agency to decide what it requires in order to do that.

The twelve-week trial, the three month trial, is does it work for any length of time that is reasonable and three months is certainly a reasonable period to consider. A year trial is

does it then continue to work, and that is going to be confounded by issues related to development of tolerance, changes in the disease process and in a host of other things.

A very reasonable question but I think a different one. One of the issues, though, that is very clear is that, in a symptomatic trial for pain, it is unethical to allow somebody to continue in substantial pain for a long period of time. What that means is that if you are talking about a trial for a year, you can't possibly expect a patient to stay in the trial if they are not getting an effect.

What that means also is that the way you would have to analyze that data would be, then, to look at success or failure, sort of a dichotomous outcome. But it would be unethical to take everybody off their medicines and have them go for a year.

There may be ways to structure it differently and I would be open for--

DR. KATZ: Dr. Rowbothom?

DR. ROWBOTHOM: There are two things that have been brought up in the last couple of minutes. One is the issue of whether or not patients can be

on other therapies that might alter their pain while they are in clinical trial. The second one is duration of treatment in a blinded clinical trial.

From the perspective of the persons that I see with these different chronic-pain disorders, it is very hard for them to see the possible benefit for them as individuals to go into a placebo-controlled trial of a drug that is, let's say, in Phase II when they have a 50:50 chance of being randomized to placebo and then they have no access to the compound open-label afterwards. So there is really nothing in it for them.

So it is difficult enough just to convince patients that, in the interest of medical science or their own agenda, to try something when there is nothing really for them at the end of the trial. Eight weeks has been long enough for many drugs to separate quite clearly from placebo and twelve weeks, certain, if you can't show efficacy over twelve weeks, then I think that the drug doesn't work for pain.

For disease modification, of course a year makes much more sense. But I think from our discussions this morning it was pretty clear that

if you focus just on peripheral nerve anatomy or physiology that that is very complicated and is only partially related to the complaint of pain.

Conversely, going the other direction, touching on what Dr. Shafer brought up this morning, is that if you follow a pure quality-of-life outcome measure, there are so many components in that--pain is just one of them--that it also makes it difficult to show that your drug is really working for pain and that is why the patients are generally coming into the clinic is they have pain and they want that to be relieved.

So I think twelve weeks is fine. I think for a patient, especially somebody with postherpetic neuralgia, to say, "I want you to be in a placebo-controlled study so you will get placebo for the next twelve months," they would say, "I am 78-years old. Twelve months is a long time for me. Thank you very much, but forget it." I just don't think I could really advocate that.

Now, if they were allowed to be on their other medications and the purpose of the study was to see if thermal-sensory function in their area of shingles pain improved, if their allodynia was going to get better, if we were going to do serial

skin biopsies to look if the nerve fibers normalized, those kinds of measures, and they were allowed to stay on other treatments and we were following purely a disease-modification type of paradigm, then I don't think that would be such a problem.

But, from a pure analgesia perspective, twelve weeks is a pretty long time for a subject.

DR. KATZ: Dr. Shafer and then Dr. Dworkin.

DR. SHAFER: Is there a role in these chronic-pain studies for the way we would approach an acute-pain study which would be essentially like an opioid sparing. You wouldn't take a patient post-op--so you don't get any pain relief but you would them on PCA morphine and you would look at sparing. Are these patients on opioids or on another drug which they can essentially self-titrate and you can use that to assess the efficacy of the new measure.

DR. KATZ: Thoughts on that?

DR. ROWBOTHOM: That has been a problem in trials, looking for opioid-sparing effect. If you look at the two initial gabapentin trials that were published, the subjects were allowed to us other

medications. They were allowed to be on an opioid, at least in the postherpetic neuralgia study. In many of the clinical trials that we have been involved in, subjects are allowed to continue using an opioid as long as it is something they previously were on and they are on relatively stable doses.

It is always possible that they are going to reduce their dose during the treatment trial and so you would be showing an opioid-sparing effect. It is a tough outcome measure to really assess because you would then be looking for a fairly restricted group; okay, I want postherpetic neuralgia, they have got to have four out of ten pain or worse and they have to be on opioids and then have one of your measures be opioid sparing.

I think that is probably cutting it too fine to be practical. I was referring really more to the ethical aspects where if you require patients to go off all their medications in order to be in a trial and then it is a very long trial with a placebo control, that is really difficult for subjects.

What you tend to get in those trials because we have done a couple of them, and this is

purely my own person experience. This is, of course, completely anecdotal; we get pretty strange subjects for those studies. You get people that either no one really believed that they had pain or everything completely and totally failed and so, therefore, they are just on nothing.

That is a bit of an unusual group. I am a little more comfortable with the--and, again, I am speaking from my experience more on postherpetic neuralgia because that is such a kind of average slice of the 55- to 80-year-old age range that they are getting a little bit of response to some things but it is not really enough at the doses that they can tolerate. So, therefore, they are interested and are able to participate in the clinical trial.

DR. DWORKIN: I would like to second what Mike said. I personally believe that three months is enough and, in fact, for a placebo-controlled study of pain--in fact, I think I could argue that, so if we are going to do three months, then that should certainly include any titration at the beginning within the three months.

I think I could argue that eight weeks would be enough to show durability. I don't know what we would get for the extra month because I am

hard-pressed to think of drugs where you lose efficacy from week 8 to 12. The original Nurontin trials published in JAMA were eight-week trials and I don't think any of us thinks that if those trials had gone out to twelve weeks that we would have lost the efficacy of Nurontin versus placebo.

So I think that twelve weeks is more than enough and I think I might even be comfortable with eight weeks.

DR. KATZ: I am going to refocus the discussion now back to the outcome measures because it is very important that we address some questions in that domain. I think that somebody said, and I don't think that anybody disagreed, that pain needs to be the primary outcome measure. I don't think we need to quibble about whether it is a VAS or a numerical rating scale or a categorical scale or whatever.

What about secondary outcome measures in neuropathic-pain trials. What would be relevant? I think that we all said that we should characterize the subtypes of pain as well to see if there is any sort of differential effect on one symptom versus another.

We spoke about measuring allodynia as an

entry criteria for characterizing our patients and I think we would all accept that as a relevant outcome measure as well. So, correct me if I am wrong. Any other secondary outcome measures that would be particularly important in neuropathic-pain trials?

Dr. Dworkin and then Dr. Farrar.

DR. DWORKIN: Some kind of measure or measures of psychological distress, psychological psychosocial morbidity, and then function, quality of life, is the patient out going to the movies and shopping more than they were before the trial began? Those would be the other two classes.

DR. FARRAR: Very specifically, those factors need to be measured at the beginning of the trial to serve as evidence that your two groups, the placebo and the treatment group, are, in fact, the same in terms of the level of depression and the level of function, and so on.

They are also vital as outcome measures not necessarily because they should be the primary outcome but because if I saw the pain getting dramatically better but people didn't do any more and they stayed as depressed or got worse, you would really begin to wonder whether it was just a

chance finding.

What we are looking for, really, is to see all of them headed in the right direction. If that is the case, then you feel much more comfortable with them. So I am strongly in favor of measuring at least those two and there is a lot of reason to think that you ought to be looking at coping mechanisms and what patients' expectations are with the trial at the base because both of those clearly influence the potential outcome of the trial.

DR. KATZ: Speak a little bit more about the expectations issue, what you are talking about there.

DR. FARRAR: This is an area that is relatively new in terms of some of the ways that it has been looked at. But it is very clear that patients' expectation for the effect of the drug influences their placebo response. If patients believe that that drug that they are going to be tried on has a very significant possibility of helping them, then, whether or not they get the real drug or not, they are going to have a better expectation for it.

The opposite is also true. If you try and enroll somebody in a trial of an nonsteroidal

antiinflammatory and they have tried it five times before and it has never worked but you are paying them $300 so they are going to do it, it doesn't matter whether the drug works or not. It is not going to work for them.

So I think it is important that you measure it up front in terms of understanding, perhaps, why the trial either succeeded or failed and then the expectation is not an issue that you would measure again as an outcome but it is very clear that, at baseline, it could have an influence over how your study ends up.

DR. KATZ: I had the opportunity to spend some time with Patrick Wall at Mass General Hospital. Just before he died, he visited Boston. He summarized for me everything that he had learned about the placebo effect in his years of researching it, in just a few words, which is that if you want to know who is going to have a placebo effect, just ask them what they expect is going to happen at the end of the trial and he can tell you right up front who is going to have a placebo effect and who is not. It amazed him that that wasn't done routinely in the clinical trials.

It remains to be seen about that.

DR. BRIL: This is not exactly an endpoint but the other thing that should be collected is safety data for all of these drugs so you have this balance between efficacy and safety and I am seeing that more with open-label extensions that are going a year or so, that people are collecting more safety data to balance against the side effects than against the efficacy than had been done before.

DR. KATZ: Dr. Shafer?

DR. SHAFER: I think this just reemphasizes perhaps ground we went over but if we are talking about strictly pain as the endpoint of the trial, then, yes, we should measure pain. But if we are back to thinking to about things that are modifying disease, then functional studies like nerve-conduction studies maybe we be the appropriate endpoints rather than just pain, itself.

DR. DWORKIN: Somehow, we have left out John's favorite measure which is also my favorite measure and that is some patient rating of their global impression of improvement. I think that is essential and awfully easy to get and may actually be some kind of integration in the patient's mind

of pain relief and quality-of-life improvement and satisfaction and side effects and psychological distress.

So that is essential.

DR. KATZ: One question comes up from time to time about the inclusion of quality of life as an outcome measure. Does anybody feel that quality of life should be a required coprimary outcome measure meaning that, let's say, for example, pain was reduced but quality of life was not changed, that that would constitute a failed trial? Anybody in the room endorse that perspective.

DR. FARRAR: I don't endorse the perspective but I do want to make the point that different quality-of-life scales have different responsiveness. If you use a scale that is not going to respond, it won't respond. So if you were going to require that, you would need to be very careful about using the right kind of quality-of-life scale designed for that specific entity.

DR. KATZ: It sounds like everybody agrees that pain is pain and we don't need to second guess it overly and quality of life is important as a secondary outcome measure but not as the sole

required primary.

DR. BRIL: How much does pain have to improve?

DR. KATZ: John, tell us. How much does pain have to improve?

DR. FARRAR: It depends on the question you are trying to answer, but if we take the point of view of the patient, I think, ultimately, the question is if you had a choice of taking this medicine or not, would you continue to take it. For a chronic-pain study, I think ultimately that is the question.

For an acute-pain study, I think the answer is a little easier because we know that, in looking at whether drugs work or not--i.e., do patients feel that they need to take an additional dose of medication for that episode. So you give somebody a study medication and thirty minutes later, it should have worked.

At thirty minutes, you say, "Is this good enough, or do you want something else?" Then they can answer. If it is not good enough, then you are quite convinced that that is likely to be the case. What we have learned from that is that a change of about 33 percent on a pain-intensity scale seems to

correlate very nicely with that outcome.

There is some data to suggest that although only in a couple of studies and it needs to be replicated.

DR. RENDELL: Just to try to rephrase the issue that I am trying to get at with the length of time of pain studies, if we are going to do pain studies, we ought to limit them to pain. But if you are going to try to add measures of functionality, it doesn't make any sense to do that in a twelve-week trial.

There is a current trial scheduled that involves two sets of nerve conductions on two separate days at beginning and end of trial. That just doesn't make sense. I don't care what nerve-conduction specialists say, you can't see a chance in that short a period of time.

DR. KATZ: Break for an official announcement. We have officially gone below our quorum if we were to need to take a vote on anything. But we are perfectly fine to continue our general discussion. Sorry for the interruption.

Any further comments on the issue of outcome measures and neuropathic-pain clinical

trials? Have we missed anything important?

DR. FARRAR: One way of perhaps getting at this issue of length of time, I think one of the primary questions in the study that you would want to look at for longer than three months is whether or not the drug continues to provide benefit because, as Mike and I think Bob, also, clearly said, if it doesn't work by eight weeks, it is time to stop.

For prevention trials, preventing progression of disease, that is a different issue, very different. In someone with pain, if you haven't created some benefit for them by eight weeks, then it is not going to work at all. What you may want to look at and, in fact, some companies now tout this in some of their discussions, which is to say, in the follow-on trial, 30 percent of the patients stayed on the drug for a year as evidence that it continued to work for that patient. I think, in some ways, that is a valid way of looking at it.

DR. KATZ: Is there a wy of making that work stand from a clinical-trial point to obtain some statistical evidence that the drug is working by influencing the disease process rather than as a

pure analgesic?

DR. FARRAR: I don't know that I can answer that question. I think it is sort of mixing apples and oranges. If we are trying to treat the symptoms, then what we are measuring is the symptoms. If you think the drug actually has an effect on the disease process, then you need to structure your trial completely differently. I think that point is valid, but if you are looking simply at pain, then I think the issues are pretty much straightforward.

DR. KATZ: Dr. Dal Pan?

DR. DAL PAN: Dr. Farrar mentioned earlier that he didn't like mean values. I was wondering if the group could just discuss a bit a responder type analysis where patients are treated as successfully treated or not successfully treated and the analysis essentially a comparison of proportions between two groups versus making inferences based on mean values of pain scores or changes in pain scores or something like that.

DR. ROWBOTHOM: That is being done quite a bit now with this number-needed-to-treat analysis where you look at the proportion who meet some criterion in the active group, subtract it from the

placebo response rate and you come up with a number, and the smaller the number, the better.

So a drug with an NNP of between 3 and 5 is considered a really good drug because that would mean that you would need to treat between 3 and 5 patients before you got one that had this level of response. So that is being done quite a bit.

I did want to mention something about what Dr. Rendell brought up a couple of times about the monitoring. I think, perhaps, there is some confusion or, if not confusion, lack of clarity or trying to do two things at once, and that is if you are doing a lot of complicated electrophysiologic testing, nerve conductions and things like that that would require an experienced person to do, and a lot of equipment, and you are doing them so close together, then what you are really doing is some kind of intensive safety monitoring rather than disease modification.

It seems that, at least what I am coming away with from the discussion today is that disease modification and pain are really different things and so trials should be designed to look at those issues separately and not necessarily try and do both at once by either doing very, very short

disease-modification studies because you can monitor pain over twelve weeks, because that is not enough time to look at disease modification, or require that studies of pain be extended to very, very long periods of time because that is how much time you need to look at disease modification.

It is probably good that they be kept somewhat distinct.

DR. KATZ: Actually, Dr. Woolf, you were on deck first.

DR. WOOLF: I terms of outcome, we haven't discussed active comparator as an element. We are talking about detecting efficacy but one issue is efficacy relative to what, just to placebo or to something that has been shown in the literature to work.

DR. KATZ: So there are a number of issues hanging in the air right now that haven't been addressed. So I am going to try to force us to address them one at a time.

Let's go with Dr. Dal Pan's question first. The advantages and disadvantages of using a mean change in a pain score as, say, the primary outcome measure for a trial versus a dichotomous response index of some kind, you are a responder or

you are not a responder and you compare the proportion of responders in each group.

Let's just deal with that. Actually, John, you have written on that so maybe you would like to summarize the advantages and disadvantages of each approach.

DR. FARRAR: I am happy to do so although I think Bob was actually first. The primary issue revolves around deciding whether a medication for symptom management works or not. I think it is important to differentiate that from one that influences the course of a disease because I think there clearly is a difference in considering those two entities.

DR. KATZ: We will focus on pain for now.

DR. FARRAR: Yes; I understand. With regards to pain specifically, the issue is that a mean value or any central-tendency value--it can be mean, median or mode--does not provide a unique solution to the idea of how many people actually get better.

The primary reason that mean values are used, at least for historical reasons, is because there is some misconception that a mean value or using a continuous analysis provides you more power

so you don't need as large a study.

There are also some issues related to how you actually then determine the effect of the study. One of the biggest criticisms that I hear is, well, if you decide that you want to do--if you do a responder analysis, you have to decide what a response is. That makes people uncomfortable. So a number of people have said to me at various points, well, if you just look at the mean value, you don't have to decide what is important. It is just statistically significant or not.

My argument is that it doesn't matter whether you get a mean or you do a proportional analysis, you have to, at some point, decide what is clinically important and you may as well do that up front.

The second issue with regards to proportional analysis or looking at a responder analysis in pain specifically is that all of our measures measure a subjective response of the patient. Since every patient responds differently and uses the scales differently, the appropriate approach, it seems to me, is to look at the clinically important difference within the patient, decide what is important for that patient, whether

it is 33 percent or being able to walk or whatever measure you would like to use, and then looking at the number of people who actually respond within the two groups.

There is a third issue which I think I have not yet been able to find a trial that actually clearly demonstrates this but at least theoretically it is possible to have a mean value that is identical in two trials and have the proportional analysis be distinctly different. There is the possibility that if you have one group that responds and one group that doesn't that we don't know a priori, that you could actually get the wrong answer using a mean value.

DR. KATZ: Dr. Dworkin.

DR. DWORKIN: We have a paper under review now that is a PHN trial. After John's paper appeared, we did the analysis that is kind of suggested in John's paper which is we looked at the proportion of responders who respond with a 33 percent reduction in the active arm--

DR. PERLMUTTER: I don't think there can be a fully general answer to that question. The answer is it depends. There are certainly situations in which you will lose quite a lot of

power by dichtomizing a variability and there are others in which you won't. My sense of what Dr. Farrar is getting at is there are methods that actually have most of the advantages of both, that you can do methods with good power which, nevertheless, can be interpreted in this elegant way in terms of responses.

DR. KATZ: Could you expand on that a little bit in terms of the methods that you are referring to?

DR. PERLMUTTER: For example, the Wilcoxin Mann Whitney Rank Sum Test can be viewed as based on the ensemble of all possible dichotomies. So someone just said a few minutes ago that one of the problems with the responder analysis is you have to decide up front what a responder is.

Well, suppose you don't decide up front what a responder is but you consider all possible definitions of what a responder is. You can actually do a statistical analysis based on all of those tests simultaneously with the appropriate corrections for the fact that you are doing all of them and sort of picking the best one.

The rank sum test and what I think is a little better than even than normal scores test can

be viewed in this way. Other methods along those lines I think can get you most of the advantages of both of the responder analysis and the purely parametric analysis.

DR. KATZ: Thank you.

DR. DWORKIN: John, I am not sure I understand the power issue because if we agree that this is an elegant endpoint that really captures what we are interested in then, if we have lost some power, so what? We just have to have some more patients in the trial.

DR. KATZ: Are you paying for them?

DR. DWORKIN: If that is the endpoint, so we pay for it. Power doesn't do it for me if we agree that that is an elegant valid endpoint.

DR. FARRAR: My guess is that the people on that side of the room probably care more about it than you do. But I would like to expand and suggest something that maybe actually we could talk about later which is that using an ordinal analysis gains you almost all of the components of other forms of regression with very small loss of power and ultimately gives you an analysis of whether at every possible cutoff--and I think that is what you were getting at--at every possible cutoff, one is

better than the other.

What is really nice about it, and we have a paper that is currently being put together on this is that you can actually draw a graph and show that--so that if Bob likes 33 percent because I told him it was the right thing and Dr. McKway in the U.K. prefers 50 percent, you can look at the graph and see the differences between the two groups at all levels. There the power issue is tiny, so I think it would even make these folks happy.

DR. KATZ: Certainly others have suggested the approach of using the parametric analysis as the primary outcome measure and then using a responder analysis which may be more intuitively understandable as a secondary outcome measure so you have potentially the best of both worlds that way.

Any other thoughts about outcome measures? Ms. Delph, did you have a comment?

MS. DELPH: As far as outcome measures are concerned, I wondered about the value of adherence to medication. The other thing, in terms of measuring outcome, does the baseline severity of disease, whether measured by intractability, level

of pain or whatever, does that matter in terms of patient population when you are assessing outcome?

DR. KATZ: I think it has become routine to use baseline pain as, in some studies, actually frankly stratifying based on baseline pain and in others at least using it as a covariate analysis at the end because that does seem to be associated with treatment response in many studies.

Does anyone have anything to add to that?

The other issue was adherence. Certainly, I would guess in most industry-sponsored trials, adherence is monitored but based on things like pill counts, I think is the standard and who knows if the patient took them or flushed them down the toilet in the waiting room.

Go ahead.

DR. FARRAR: A quick comment. A friend of mine down the hall studies HIV in patients and where adherence to the use of drugs that make patients feel really lousy is a big issue. The advantage we have in pain management is that if you have got a drug that makes people feel better, there is no problem with adherence.

MS. DELPH: Which is why I am asking whether it would be valuable as an outcome measure.

DR. FARRAR: I don't think so. I think whether they take them or not is going to be dependent on many, many different factors and what you are really looking for is efficacy since you know that patients who get better are going to take the drug. I don't think it is an issue of trying to figure out whether the ones who don't get better don't take it. I think it is really an issue of whether they feel better or not and how you measure that.

DR. KATZ: I actually wonder whether--certainly there is experience in other areas of clinical trials where adherence is a huge issue and trials have failed because people have side effects and don't take their medications. There have been a variety of approaches that have been used and I am sure the folks from the FDA know a million times more about this than I do but, for example, putting inert markers in tablets and measuring urine tests to make sure people are taking their medication, having bottles that it records it digitally when you open the bottle.

Of course, you can open it and flush it down the toilet again, but it still gets you one step closer to understanding a true adherence,

diaries for medication consumption, that sort of thing, because a small number of nonadherent patients in the treatment arm can completely distort the end results of the trial. But I don't know how commonly--I don't think these things are commonly done. I don't know what the regulatory perception is about how big a problem it really is in actual practice.

DR. McCORMICK: I think they are fairly commonly done in trials but I am not sure how much we really use that information. I think the point was a good one that the fact that patients who don't take their medications don't respond doesn't really help us in the end.

Dr. Hertz just pointed out that more frequently than not, if patients are not tolerating the drug, they drop out of the trials.

DR. ROWBOTHOM: I just wanted to make one comment picking up on what you are saying. It is not really about adherence, per se, but it is an important one and that is if you are following and intent-to-treat type study and data analysis, then the patients who are either not adherent or who drop out of the study, they are still counted by the outcome.

Some of the trials that have been mentioned during the day today are problem trials because they didn't follow an intent-to-treat analysis. They only looked at the subjects who completed the entire study.

So if you take a study and you break down the data and you look at the patients who completed everything and leave out the data from the subjects who didn't complete, then you will get very different results and it will usually overestimate the treatment benefit.

DR. KATZ: Dr. Perlmutter?

DR. PERLMUTTER: I agree with that. I just want to say there are some good ways, I think, of taking adherence to treatment into account in the analysis of trials without violating the intent-to-treat principle, but I agree with you completely that the way to do that is not just to leave out the nonadherent patients.

DR. DWORKIN: Your point, Ms. Delph, made me think of something we haven't discussed which is that industry seems to have consensed on an average pain rating of 4 or greater for entry into these trials in a kind of baseline week of ratings.

So now I am going to say something that is

going to make me even more unpopular on that side of the room. When we place ads in newspapers or get referrals from primaries, there are a whole lot of patients who come in and fail entry criteria because their baseline weak of pain ratings is a 3. So their average over seven days is a 3 and they are not close to the 4 required in these trials. And those patients are real disappointed that they can't participate in the research.

To my mind, that begs the question of whether we are setting the bar too high. Now, I realize there is going to be a loss of power if we set the bar at 3 or even 2 or 2.5, but there are a lot of people out there with chronic pain that we might say is in the mild to moderate range who desire treatment enough to be interested in enrolling in a placebo-controlled trial and we are excluding them from all ongoing studies that I am aware of.

DR. KATZ: Thoughts on that issue? You are correct in that there is literature suggesting that there would be a loss, a floor effect and a loss of power from dropping below there.

Dr. Farrar?

DR. FARRAR: I had a patient that I

treated who had the worst pain I had seen in years and his pain was never worse than a 3. The reason is because on the worst end of the scale, he imagined his father in a concentration camp and that was enough to move him all the way down the scale. So there clearly are people who use 3 or have 3 as a measure who have intensely bad pain.

The issue, I think, primarily is that you have to have enough of the scale to move in order to be able to accurately measure the amount. One might be able to put patients in who are at a 3. If my data is correct and 33 percent is a reasonable drop, then going from 3 to 2 would be 33 percent.

The trouble is you get to 2 and it is 50 percent or nothing. So you end up losing the ability to be able to differentiate that. We could argue about 3 and 4, but I think the issue is not whether there aren't patients that would be good to have in the trials but, rather, a measurement issue and that makes it sort of the reason we have to stick with that.

Wrapup

DR. KATZ: We are now officially in the wrapup phase of our session. So I would like to

turn to the FDA folks and ask them if they would like to focus the discussion in any particular direction.

DR. McCORMICK: Actually, I have one question that is an extension of the debate that we heard earlier and the discussion that surrounded that debate. You have all received a copy of the guidance for industry on the burden of evidence, of establishing evidence in clinical trials.

The writers of the guidance envisioned situations in which a single clinical trial might be used to--when an indication had already been established, to extent that indication of there was sufficient pathophysiologic similarity across disease states to warrant that.

I guess my question for the committee is--and I feel that we haven't quite come to closure on the lumping and splitting. I feel that is still up in the ethernet somewhere--that my further question is do you think that this group of diseases or disorders that manifests themselves with pain are sufficiently similar such that we might be able to, let's say if we have had an indication for postherpetic neuralgia and then we have another single clinical trial in another

neuropathic pain state that that might be sufficient to get a claim for that other disorder, not necessarily a broad general claim for neuropathic pain but an additional condition.

DR. KATZ: Thoughts on that? Do people feel that if you have, for example, two adequate and well-powered trials for a painful diabetic neuropathy showing a very believable successful result and now you have got another trial that comes along, single trial, postherpetic neuralgia, very believable, should that be sufficient to hold in abeyance this replicate-trial rule and would we believe that that drug is probably efficacious in postherpetic neuralgia based on a single trial?

DR. McCORMICK: I guess the follow up to that is what evidence would you need to be able to say yes to that.

DR. KATZ: From the specific trials that have been done.

DR. McCORMICK: In that specific trial.

DR. BRIL: I would accept a single trial as an add-on to another--I would lump that far. So if you had two replicate trials in one indication and then a very robust trial as well as in another indication but a single one, I think there are

enough similarities in neuropathic pain to enable that to happen.

We were going to lump all neuropathic pain. So this is similar enough to me and the same level of evidence you had in one of the two trials that were for the original indication, if you had that in another indication, I think that would be good, so a 33 percent pain reduction or a responder analysis or whatever particular measure was being used in these trials, I am not sure you would need to replicate that.

DR. KATZ: You would want to see, though, that there was a satisfactory clinically meaningful effect.

DR. BRIL: Oh, yes.

DR. KATZ: As an example of robustness.

DR. BRIL: It would have to be a robust study. If it were weak or marginal or uncertain or there was criticism of the study for some reason, the patient population was skewed somehow or it was all in one center--there are things that would limit it but if it was a multicenter, well-run, well-powered study with well-defined patients and the results were very clear and unequivocal and replicated what had happened in the other two

trials, I that would be acceptable.

DR. DWORKIN: I am uncomfortable with saying yes to your question, Dr. McCormick, and so I will answer it with a question. I don't know what the precedent is for SSRIs. If I have two positive trials, say, for generalized anxiety disorder with my favorite SSRI and I think do a positive trial in social anxiety disorder, is the precedent that that gets me the second indication?

I think if the precedent is yes in the context of anxiety disorders, then I would be more comfortable in going from two positive PHN to an additional indication for DPN if it is positive. But if the precedent in anxiety disorders is no, then I wouldn't be comfortable in our domain.

DR. McCORMICK: I can't comment on the precedent for anxiety disorders but I can comment on epilepsy trials where an indication has been granted in many trials in many of the drugs that we have for complex partial seizures and then a single trial in Lennox Gasteau was granted based on--an indication was granted for Lennox Gasteau based on a single trial.

DR. DWORKIN: But isn't it the case that the percentage of failed trials in things like

depression and anxiety is much higher than in epilepsy?

DR. McCORMICK: Yes.

DR. DWORKIN: And probably the better analogy for precedent would be psychiatric disorders than epilepsy for neuropathic pain. I guess that is the way I was thinking because my understanding is that the packages for SSRIs in depression had as many negative trials as positive trials.

DR. KATZ: But just to focus on the issue at hand, Dr. Dworkin, if you had two trials sitting in front of you that were adequate and well-controlled for painful diabetic neuropathy that you had no questions about and then another one came along in postherpetic neuralgia, enough of a sample size, results seemed robust, what would you believe? Would you believe that that drug was likely efficacious in postherpetic neuralgia or not?

DR. DWORKIN: I am uncomfortable. I would want to know if other trials had been done in that indication and what the results were.

DR. KATZ: They haven't.

DR. DWORKIN: They haven't. I don't know

what other people think. I would be uncomfortable.

DR. KATZ: Would that be a yes or a no?

DR. BRIL: He is a splitter.

DR. DWORKIN: It is a no. I'm a splitter.

DR. KATZ: Dr. Woolf?

DR. WOOLF: I actually did do my homework and I read it and it seemed to positively exclude symptom control, the guidelines. It specifically said for life-threatening or serious--is that true? Are these the criteria for a single additional trial? I do remember it saying symptom control was not envisioned as being--

DR. McCORMICK: I think, in this particular section, studies in closely related disease, it really was not referring to terminal illnesses or serious life-threatening diseases, but in general.

DR. FARRAR: Bob's question and Nat's pressure to answer does raise a question that fits in with what you have asked which is getting a positive trial, a single positive trial, given the nature of p-values, does suggest that at least in 1 out of 20 products you might get a single trial that is positive by chance.

One of the questions, then, would be if

there were a bunch of negative trials and then a couple of positive trials whether that becomes adequate for an indication. I honestly don't know how that fits with your criteria in terms of the initial indication and then subsequent indications.

DR. McCORMICK: I think we would weigh the evidence.

DR. KATZ: Any other thoughts on this single-trial issue? Dr. McLesky?

DR. McLESKY: I was just going to say, in response to Clifford's comment, that I was pleased that the guidance was delivered to us to read and, in fact, to help focus us. From my reading of it, Dr. McCormick--you are the expert in this, but from my reading of it, it seemed to imply that there is judgment left with the agency to determine, in that particular drug class and in that particular patient population and disease groupings, if it does make sense to have just one single trial for a new indication or a new patient subunit tested.

That is really the question I think that the FDA would like to hear answered here. Are you comfortable in this group of disease states? Are they similar enough, if there is good evidence with a specific drug, to have that drug then, if there

is corroboration in another kind of a similar disease state, are you comfortable having that indication spread over?

DR. KATZ: It seems to me that false-positive clinical trials in neuropathic pain are unusual if they exist at all. To have a clinical trial show that a drug works for neuropathic pain but then find that, through some subsequent process, clinical practice, surveillance studies, you know, what have you, that it actually doesn't work.

Can anyone think of an example of that? Maybe dextromethorphan is the one example I can think of which I swear it doesn't work at all in clinical practice but there are trials. But if you look at the details of those trials, they would not meet what one calls robust criteria of any sort, I don't think.

Mexiletine? No, again, I think that is a debatable point. I have a number of patients on long-term mexiletine treatment. You agree with that? So I don't know. I think that my own understanding of the literature and what I have seen, and I would welcome other people's perspective on this, that I am not aware of a true

false-positive trial where a single trial appears robust but then the medication winds up actually not being efficacious in clinical practice. I am not talking about the things that eventually come off because of safety reasons.

Does anybody disagree with that? Dr. Rowbothom?

DR. ROWBOTHOM: I was going to say yes to your earlier question that Bob was having such difficulty with saying yes or no. But I will say yes to that one. Obviously, it is going to get more complicated if, let's say, a very similar drug was studied in that disorder and proved inactive or if you were in a situation where there are now multiple studies, some positive, some negative, and you were trying to get a second indication.

That, of course, goes to the agency to sort out but if you have--the premise, as you stated it, I have no problem with. I think the only comment I would make in response to or in follow up to my yes is that I think you still want to try and encourage study, if not to establish efficacy, to at least look at safety and tolerability in some of the less well-understood or seemingly less-responsive disorders so that we can

get out of the current cycle we are in where there are really only a few neuropathic-pain disorders that are being studied and a very large collection of neuropathic-pain disorders that are going unstudied.

DR. KATZ: Clearly, your point about safety is worth--a trial that would satisfy us with a demonstration of efficacy would not necessarily satisfy us with a demonstration of safety in that particular population.

Dr. Dworkin?

DR. DWORKIN: I guess an example that occurs to me and that is carbamazepine where there is an indication for trigeminal neuralgia and there are four or five trials that are inconsistent among themselves in diabetic neuropathy. By this criterion, given that there is an indication for trigeminal neuralgia, the existence of one or two positive trials in diabetic neuropathy should give carbamazepine an indication for diabetic neuropathy.

But my sense, and you guys know much more than I do, is no one thinks that carbamazepine is an especially efficacious drug in diabetic neuropathy or that we don't know what the answer is

to that question.

DR. KATZ: I think it is not used that much because there are agents that are more well-tolerated that don't require monitoring of blood tests. I don't have, myself, any reason in my own experience to think it is not efficacious. Do you disagree?

DR. ROWBOTHOM: I would agree with what you are saying but also I don't think that any of those studies of carbamazepine for diabetic neuropathy would meet at least my conception of the hypothetical situation you were putting forward. Those were not large robust well-controlled studies. They were mostly older studies, smaller, and they don't really meet the current criteria for how good multicenter properly controlled clinical trials are conducted.

DR. KATZ: It sounds like what you are saying is that it does get back to the judgment call and that there are circumstances where the robustness of the program of the whole and the lack of any other negative mitigating factors could give the agency reason to approve that second indication from just a single positive trial.

Yet there are other circumstances where a

trial that might not be so strong or that might be contradicted by other evidence would allow them to make a judgment against that second indication. Is that more or less what you are saying? Does anybody disagree with that perspective that there are circumstances where a second indication could be given based on a single positive trial in the right circumstances and that it shouldn't be absolutely ruled out? Do you agree with that, John, Clifford?

DR. FARRAR: Yes; I do. I think the issue is how you define robust and, just to be absolutely clear, it has nothing to do with the statistical significance. So, provided that there is adequate evidence that it really creates a clinically important improvement in the patient population, I have no problems with it.

DR. KATZ: Clifford?

DR. WOOLF: Because, as we recognize, there will be a 1 in 20 chance of a false positive, I feel just a little bit uncomfortable. I would feel much more comfortable if there had been two replicate studies of diabetic neuropathy and postherpetic neuralgia and then a third one for radicular. Then I would be very comfortable.

DR. KATZ: Everybody wants to be comfortable. Ms. Delph, you had a comment?

MS. DELPH: I have a question for the FDA. Does the indication have to be an all-or-none, yes, it is indicated or no, you don't give the indication or can you, in the labeling, give the clinical-trial information that is available and give some conditional indication that it may be or under some circumstances or that kind of wording.

DR. McCORMICK: I didn't catch the first part of your question which I think defined what the results of the trial were.

MS. DELPH: No; sorry. I think we are assuming that you have two good trials that give a particular indication and then a third one that is scientific sound that gives a possible second indication. What I am asking is, for that second indication, does it have to be all or none? In other words, do you either give the indication or not give it or, in the labeling, can you indicate that this is the scientific information available to us and, therefore, it may or may not be indicated in certain individuals with this condition.

DR. McCORMICK: First of all, by a

possible indication or possible positive trial, do you mean that the results are equivocal in the trial or the results are positive and we are the point of deciding whether or not to grant the indication.

MS. DELPH: Yes; that is what I am saying. You have the one trial and the results are unequivocally positive in that trial.

DR. McCORMICK: The reason for asking this question now or beforehand is because we really need to know what our criteria are for granting an indication. We really don't give provisional indications in the labeling. We either have to make a determination at the time of approval that the drug will be indicated for that condition or not. We can't really say, "You decide." That is really not an option. So we really have to make that determination, do we have the grounds, based on the evidence that we have before us, that this drug will be indicated for that condition. That is why we are deliberating about it now.

DR. KATZ: In the few minutes we have left, I wonder if we could address the issue that Dr. Farrar mentioned earlier which is the whole issue of adjunctive therapy because that comes up a

great deal and there are a lot of important implications.

So, for example, you want to do a trial on Drug X for neuropathic pain but we know now that, let's say, for postherpetic neuralgia, we know now that gabapentin is effective for postherpetic neuralgia. We know that amitriptyline is and other tricyclics. Can we justify withholding those medications from people? Can we carry out a clinical trial that is likely to show efficacy when the patient already has other analgesic medications on board?

If we did decide to do that for ethical reasons, would we then be granted a label for adjunctive therapy and not monotherapy which I think many sponsors look at as a potential albatross. What do people feel about those issues? Everyone is numb by now.

DR. BRIL: I would like to see some adjunctive studies because I would think that some of the medications could be synergistic and you may have more relief than you would have with either alone. However, for the reasons I said before, I think it is more difficult. You may pick refractory patients who are going to fail to

respond. If patients are already on a drug or two and they still have a lot of pain, usually I am very pessimistic about their outcome.

So, although I would like to see adjunctive studies, I think that monotherapy is probably the initial thing for a new drug for diabetic-neuropathy pain anyway and then, perhaps, there could be some requirement or suggestion that adjunctive studies--or that there be an adjunctive arm, there be a placebo arm, a single drug arm and an adjunctive arm, something of that nature.

DR. KATZ: So even though that wasn't necessary for an indication, an adjunctive--I mean, that is a separate thing. But, still, I think we all would like to see data on potential synergism. Do people feel that it is ethical to have patients off of neuropathic pain medications completely for twelve weeks now that we know that several of them are efficacious? Dr. Farrar?

DR. FARRAR: I think Mike actually alluded to this earlier which is that if a patient with diabetic neuropathy is 100 percent better on a drug, they are not going to volunteer for your clinical trial. I think what you are going to get is patients who got 30 percent relief, some percent

of relief, but not adequate relief from, say, tricyclic antidepressants.

In a setting where the drug you are going to be testing can be demonstrated to be safe in the combination, and that is obviously the issue, I would argue for doing the study allowing patients to come into the study on whatever they are on, stay on whatever they are on for the period of the twelve weeks to see whether what you are using makes them better or not.

The argument is that, I think, if you have--or the argument would be that if you have patients who are completely cured by one particular drug, they may remove from the population people who are more responsive. I think that is true. But I don't think that gets away from the ethical issue of if something is helping a patient a little bit, it is hard, ethically, to take them off.

You don't lose anything, I think, by trying to treat them with a second drug as long as there is not an interaction.

DR. KATZ: Granted that there may be an ethical advantage of allowing patients to remain on their baseline medications even though their provided only partial relief, you would advocate

adding on the study drug or placebo to what they are on. What type of indication would such a drug get? Would it be indicated as adjunctive therapy with--

DR. McCORMICK: If you were to lave patients on their existing medications and then do a placebo-controlled trial with the new agent, then they would get an indication for adjunctive therapy.

DR. KATZ: Even if they were on a hodge-podge of different medications.

DR. McCORMICK: Even if they were; right.

DR. KATZ: So how do we deal with that problem?

DR. DWORKIN: Even if those medications have no indications for this condition?

DR. McCORMICK: That's a tough one.

DR. DWORKIN: They are on tricyclics which don't have an indication for neuropathic pain.

DR. McCORMICK: In reality, I think that they are being used to treat the pain. I think what we would probably do is describe that in the labeling.

DR. FARRAR: To try and be concise about it, there is a tremendous argument in the

literature about whether it is even ethical to do studies with placebo in pain-related clinical trials. I would have a great deal of difficulty getting a study through my IRB that said I had to take a patient off something that they were already on that was working at least partially for them.

What I think may be the mechanism is what is used in epilepsy trials which is that the initial study is an adjunct study and then, at the end of the study, if patients get dramatically better, you can say, let's take you off of the tricyclic and then show that they continue to have benefit, showing that monotherapy ultimately provides them with the benefit.

Now, I don't know how to structure that trial specifically with regard to regulatory issues but that would certainly convince me.

DR. McCORMICK: Actually, the way those trials are usually done, or usually what happens in those scenarios is that the product has demonstrated efficacy and then subsequent trials were done as monotherapy. You don't have the withdrawal effect or issues of crossover.

DR. KATZ: Other comments about the adjunctive therapy issue?

MS. DELPH: I find it very difficult to agree with taking patients off medication that is working for them without proven efficacy of the investigational agent. I like the suggestion of the design that you are giving. I know, statistically, when you start involving other agents, it is a nightmare. But I also wonder about things like crossover trial designs, whether those would be useful.

DR. KATZ: It is clearly a complicated issue and crossover trials have their own baggage that makes them frequently difficult to interpret. It is interesting to note in the context of taking patients off their medications that many of the trials that I have seen in osteoarthritis and similar indications where people are taken off their baseline medications, there is a flare. They are enrolled in the trial and they get put on either an active treatment or placebo, the patients in the placebo arm typically have at least as good pain relief as on their previous acting drug if not actually better. So I am not sure that, in real life, there is actually any consequence of taking patients off medications that they think are working for them.

I don't know if it is the fact that they are in the loving hands of a clinical-trial unit or if the drug was actually not that efficacious for them, but I am not sure if it is more of an imaginary issue or a real issue.

DR. BRIL: I think, in practical experience, if you have a patient who is doing well on drugs, you don't take them off them because the response rate is so uncertain. If you have someone who is responding to therapy, you don't really put them into these drugs. It is the people who don't respond, who are on drugs, they are not any better. They still have a lot of pain and those are the patients who will come off their drugs because they are not helping them anyway.

Usually, yes; these are short-term trials. This is why they are short, I guess, and you usually have rescue medications and then you have dropouts. So there are ways to handle the ethical issue of having a placebo arm in the trial, or ways of considering it, that I think are fairly ethical.

But it is not standard practice to have someone who is well-controlled and take them off their pain medications and put them in a pain trial.

DR. KATZ: It is hard to be prescriptive about that, I think. I think that when I was seeing patients actively, I would spend as much of my time taking people off medications that they thought were working but, in retrospective, weren't after they came off than I did putting people on medications. So I think it is often very difficult to tell and patients are often wrong about whether medications they are on are actually helping them or not.

I think it is hard to be prescriptive.

Any final comments about any important issues related to neuropathic-pain clinical trials? Any final questions from the FDA side of the table?

DR. McCORMICK: I would like to thank the committee for a wonderful discussion today. It has been a great honor to have such distinguished guests here with us sharing your thoughts. Thank you very much.

DR. KATZ: Let me thank everybody as well for a wonderful discussion and we will see you next time.

[Whereupon, at 5:30 p.m., the meeting was adjourned.]

- - -