the strong point that we have to do better in being able to get a larger fraction of patients to target and that it's hard. A lot of the existing agents in a lot of patients are unsuccessful. Yet, it seemed in this trial that there was a large fraction of patients in which there wasn't even the attempt made or the additional -- in the population here in table 5 in the FDA briefing document, it looks like there are approximately 20 percent that received adjunctive treatment in weeks 9 to 14 and large fractions in the first 8 weeks didn't get to maximal dosing.

So, that seems to be perplexing. It seems like in the majority of cases we're not taking advantage of what there already is available to us to achieve what you're saying we need to achieve. It's not a matter of they're trying it and it's not getting there.

DR. BLACK: I think that worked in both arms of the study. You didn't get to 90 or 100 percent control rates in the omapatrilat arm either.

DR. FLEMING: In both arms.

DR. BLACK: In either arm. And that's only 6 months. Ours is a year. The trials are 4 and 5 years. So, there are several different ways to look at that.

I don't think that's how people practice. We have an education message for that as well, but I'm not sure we can manage even with what we do in trials or what

happened here to get people to practice as we would like them to do it. I think a couple of extra millimeters for each one of our steps is going to get us much further along the road. We've got a lot of education to do beyond what you see here to get people to use what we have right and to have a more powerful tool to use that right.

The NHANES IV data is kind of almost done. NHANES III is where the 27 percent comes from. There's been a big national campaign to improve control rates, and it's been, at best, only modestly successful. We've improved control rates in men to about 30 percent, which is about what women get, but nowhere near what we ought to. So, there's a lot to still be done. I think we need better agents. Even with the optimal circumstances of a trial or of a specialist clinic, we're still not where we want to go.

DR. TEMPLE: That's what I understood your argument to be. You're basically saying how can we not do better if we have a drug that works a little better than the thing it's going to substitute for. And maybe that's sufficient. I'm not trying to prejudge this, but that's not the same as saying in a population where we couldn't get control, here's what we know about substituting versus, say, adding another drug. It's a question of whether you need data on that point or have data on that point as

opposed to making some not necessarily unreasonable assumptions.

DR. LEVY: Let me just make two points. We freely concede that in patients who can readily be brought to target with the addition of a thiazide or up-titration of an existing drug or a switch to b.i.d., that this drug is not needed. The drug is being proposed for use in patients in whom the option of adding another drug or adding another drug and reaching target isn't available.

Now, physicians in this trial, as you pointed out, didn't invariably add adjunctive therapy when it was available to them. They did so about 40 percent of the time, and they were much more likely to do so in patients whose blood pressures were well above target on monotherapy than in those who were closer to target, just as physicians in practice would. But there's a wide variety of practice represented in the trial.

What we did here was just to classify the investigative sites according to the aggressiveness of the physician, how frequently did they add adjunctive therapy at a visit where a patient's blood pressure was above target? These are 20 percent of sites, the quintile, where the rate of adjunct use was highest, and these physicians I think were very diligent adding adjunctive therapy at least two-thirds of individual visits where patients remained

uncontrolled, up to 100 percent at some sites. And even at these sites, you see the same difference in blood pressure reduction between omapatrilat and enalapril that you see overall. You see the same difference in control rate.

This speaks to Henry Black's point. In the difficult to treat patient, if the physician decides to become more aggressive, add therapy, up-titrate, they're going to do that whether the patient is on omapatrilat or enalapril, and the results will be better with omapatrilat.

DR. FLEMING: But that's not in your targeted subgroup. That's all patients at the sites that had the highest adjunct use?

DR. LEVY: These are roughly 2,000 patients at the 20 percent of sites where the physicians were most aggressive.

DR. FLEMING: So, what were the results at those sites that had the highest adjunct use that were in your target population? What were the results?

DR. LEVY: Well, we haven't done that analysis. You've seen the results were extremely consistent across this database.

DR. BORER: Tom and then Steve.

DR. PACKER: Jeff, if I could, I just want to address directly Bob's question. You've seen the data that Dr. Levy just showed you, but this shouldn't be too

surprising and I wouldn't be surprised if it were shown in the patient population that was being proposed. The concept I think is that if you have a patient who has easy-to-control blood pressure and you can get people to target, then I think it would be a very easy assumption to say that the difference between omapatrilat and an ACE inhibitor could be made up by adding a diuretic. No big deal.

But if patients are very far away from target, then a diligent physician, a really good physician, would then add incremental therapy or give b.i.d. or however you want to do it to both groups. The difference in blood pressure only disappears if there's a differential use of adjunctive therapy or intensive therapy. But that differential use would never occur if you're not to target. You would expect a patient who is resistant to therapy to -- the physician would add adjunctive therapy or optimize dose or would do whatever you would want them to do to both groups. As long as they're far from target, the difference in favor of omapatrilat would always persist.

DR. TEMPLE: So, that's an argument of logic, although it's not necessarily an argument of data, although that last thing was interesting.

DR. PACKER: Yes. But if you think about it as the fact that in order for the difference to disappear, there has to be a differential use of adjunctive therapy,

which cannot -- and by the way, to a substantial degree, the calculations that Norm Stockbridge made was 50 percent difference in differential use. Regardless of what the number is, the number isn't important. As long as you're far away from target, that differential use won't happen, especially if you're requiring people already to be on multiple drugs at the beginning.

DR. TEMPLE: It's still a question of whether that makes sense, which I wouldn't say it doesn't, and whether there's actual data so you can see actual numbers about how much better you do.

DR. PACKER: I think what I'm addressing is not whether what I'm saying absolutely has to be true, but I think you were struggling with how it could be true. What I'm proposing is that's the explanation for why it would be true.

DR. BORER: Why don't we move on to another issue. Tom.

DR. FLEMING: Can I have one last comment?

DR. PICKERING: It is actually a related issue. Starting with the possibility that if OCTAVE had been continued longer, the difference might have diminished, my reading of the protocol was that there were only two clinic visits at which it was possible to add additional drugs, which in my opinion is not very long.

Henry, you mentioned the ALLHAT trial. I don't know if we could see your number 6 slide which shows that using conventional therapy in not perhaps quite as high a risk population but certainly in an enhanced risk population, you can in fact do extremely well, going from 27 percent to 69 percent control at 6 years. I guess it's a question of whether you see the glass is half full or half empty, but I would say that's a huge increment just with the use of conventional therapy.

DR. BLACK: I would agree. I think we did make a lot of progress, but I think there's still a lot more progress to be made especially in what we don't have the tools for. These people are seen every 4 months.

One thing too, when you begin to add third and fourth and fifth drugs, you get into less well-tolerated drugs, drugs with their own inherent problems too. It's not just adding drugs that are free of side effects when you get to that, and patients don't comply well with that. So, we begin to run out of well-tolerated options a little earlier than maybe has been implied.

But we're not doing badly here, nor did we in CONVINCE, but we're not doing nearly as well for systolic as I would like to do. That's where the problem is I think.

DR. BORER: Bob.

DR. TEMPLE: Well, Henry, if I remember ALLHAT, the additional therapy was sort of peculiar. For example, if you were in the diuretic group -- you tell me -- you couldn't use an ACE inhibitor because that was another group and that would have confounded. So, you were limited in the number of specific additional drugs you could use.

DR. BLACK: The trial protocol -- the artificiality of any active comparator where you can't use what you would ordinarily use --

DR. TEMPLE: No, I'm not blaming the trial. But it means that may not be as good as --

DR. BLACK: What you could do, though, if you felt you needed it, was add an agent of the blinded class at half the initial dose, drop down your drugs. So, you could do it. I don't have the drug use in ALLHAT yet as to how many people got on open-label, how many people crossed over, but it was in fact substantive. It wasn't just that you couldn't do it. People did use their own drugs.

DR. BORER: Steve.

DR. NISSEN: I feel compelled to point out for Bob and for others, which I know everybody here knows, but we don't know whether that extra 3 over 2 millimeters for this drug actually lowers events. So, this is all hypothetical, what if we did this and what if we did that. The reality is if there were a very large difference

between the arms, I think one could be more confident, but these are small differences. Therefore, without knowledge of the relationship for this class of drugs on the amount of blood pressure control versus morbidity and mortality, we're really speculating about what the ultimate impact is going to be.

DR. BORER: Are there any other questions, issues the committee wants to raise? Because if not -- Tom.

DR. PICKERING: I'd like to return to the issue of adherence. I think we're all agreed that omapatrilat is a more effective antihypertensive than the other existing drugs. One of my concerns is what the adherence will be with this medication, given all the warnings and education about potential risks. It could be that the potential benefits in its potency might be offset by decreased compliance.

On that note, I think it's just worth mentioning that patients' self-report about compliance with antihypertensives is generally thought to be next to worthless. Pill counts are maybe a little better, but a lot of the pills end up in the parking lot of the hospital of people in studies. So, I think it is a real issue, and I would be concerned about this.

DR. BORER: We'll structure the remainder of

our discussion around these questions. I want to frame them before we begin. I think, although the questions are reasonably straightforward, there are some key issues about which we need to make judgments.

First -- and Tom just mentioned this -- is are we convinced that omapatrilat is more effective within the labeled range than other available antihypertensive agents so that one might expect that it could add something. And a subset of that is does it add to other drugs that might be given at the same time.

Second, is there a population that could be controlled by omapatrilat that cannot be controlled with all the other conventional therapies and approved therapies that we have?

Third, if there is such a population, can we define it?

Fourth, if there is and we can and we do give the drug and it does lower blood pressure by some amount, is there a clinical benefit associated with that, something what we really have never required anybody to show and maybe we can take on faith. But the issue still remains as Steve has said several times.

Finally, assuming that lowering blood pressure is equivalent to a clinical benefit, what are the risks associated with gaining this benefit in the specific group

that we have defined that couldn't be controlled in any other way than by adding omapatrilat? That's really the sequence of issues that we have to face and we're going to face them in different ways in these questions.

Bob.

DR. TEMPLE: If you got to that point, you would also really need to address the risk management program and whether you think that will do it. We have people here who reviewed the risk management program who could comment further than what they've already written, if that were helpful.

DR. BORER: Ultimately, presumably that mitigates to some extent or may mitigate to some extent the total risk, and if you believe there are FDA comments about that, then perhaps when we get to that question, we'll ask for the comments.

DR. TEMPLE: Well, you've seen some of them.

DR. BORER: Yes.

DR. TEMPLE: There's a fair amount of skepticism probably noted.

DR. THROCKMORTON: It's important for us to hear some comment around that I believe not perhaps specifics that this one thing you think works or whatever it is, but what you said, Jeff, was perhaps it reduces the risk or changes the risk somehow. We need to understand

whether there's sort of a belief that that is possible or is not. Again, not necessarily that you know the exact right answer but that you are optimistic about those things as possible would be something we need some help on.

DR. BORER: You'll hear it.

Why don't we then begin. What I'd like to do, I'll read the preamble here, and then as we go through these questions, I'd like to hear Tom's response first, Tom Pickering because he is a nonvoting member, and then we'll go to Steve who's our committee reviewer and then to Tom Fleming and then the rest of us.

The committee is asked to provide an opinion on the approvability of omapatrilat for hypertension. Omapatrilat is an inhibitor of angiotensin-converting enzyme and neutral endopeptidase. Reviews of chemistry, pharmacology, toxicology, and biopharmaceutics present no apparent barriers to approval. Omapatrilat clearly lowers blood pressure.

During its initial development, an increased risk of life-threatening angioedema was noted for patients taking omapatrilat compared with other antihypertensives, including ACE inhibitors.

To characterize this safety finding and to gain additional information on the relative antihypertensive efficacy of omapatrilat, the sponsor conducted the OCTAVE

trial.

OCTAVE was a randomized, double-blind study in which 25,302 subjects with hypertension were randomized to once-daily enalapril or omapatrilat and followed for 24 weeks. During the first 8 weeks, subjects were titrated to a maximum dose of 40 milligrams enalapril or 80 milligrams of omapatrilat as needed, after which subjects who did not achieve the blood pressure goal could have additional antihypertensive agents added through week 24. At 8 weeks, 41 percent of subjects in the enalapril group and 33 percent in the omapatrilat group were on the highest recommended doses. Between weeks 8 and 24, 19 to 36 percent of the enalapril subjects and 13 to 26 percent of the omapatrilat subjects added antihypertensive therapies. At 8 and 24 weeks, omapatrilat had a significantly greater effect to lower trough blood pressure compared with enalapril, but angioedema, including serious angioedema, was significantly more common in subjects taking omapatrilat. And we have a table outlining those data.

With these results and the data from the other trials of omapatrilat, the committee is being asked to characterize the risks of omapatrilat, to identify and characterize the benefit to which this risk needs to be compared, and to discuss whether omapatrilat's benefits outweigh its risks.

So, we'll begin. How should one best characterize the risk of angioedema with omapatrilat? 1.1. Are the clinical features of angioedema associated with omapatrilat similar to those associated with approved ACE inhibitors? Tom.

DR. PICKERING: Well, I think we've heard quite convincingly that the clinical features are generally similar, although with omapatrilat, the extent of the angioedema is more likely to be severe.

DR. BORER: Is it not true that the angioedema tends to occur earlier also with omapatrilat than with the ACE inhibitor?

DR. PICKERING: Yes, since most of the episodes did occur during the first day.

DR. BORER: Are there any other comments about the characterization? Steve.

DR. NISSEN: I want to emphasize that there's a pretty steep gradient here compared to enalapril in terms of the risk ratio for mild, moderate, and severe. So, it really looks like there's a significant shift from the more mild forms to the more severe forms. So, it's not just a quantitative measure. It's really also I think a qualitative measure which I think you were saying also, Tom, that there is disproportionately more severe angioedema with omapatrilat.

DR. BORER: Any other opinions?

(No response.)

DR. BORER: Then let's go to 1.2. In the original development program, about twice as many subjects were exposed to omapatrilat 20 milligrams than to 10 milligrams as an initial dose, and the rate of any angioedema was about three-fold higher in subjects initially receiving 20 milligrams. OCTAVE's primary safety hypothesis was that starting omapatrilat at a low dose and titrating up would reduce the risk of angioedema of any severity to no more than twice that of enalapril. Was this hypothesis supported by the study?

I don't think this needs much discussion. It wasn't. Is there any dissent from that?

(No response.)

DR. BORER: No.

1.3. In OCTAVE, there were two cases of life-threatening angioedema among 12,000 subjects treated for about 6 months. In the original development program, there four such cases in a population about one-third as large. Estimate the risk of life-threatening angioedema to expect post-marketing and estimate the upper confidence limit for that risk.

I think in fairness maybe we better begin with Tom Fleming for that one, and then go back to Steve and

Tom.

DR. FLEMING: Well, let me respond to this and add a little bit of response that relates to question number 1.2.

The sponsor has provided us the estimate with these two cases that the upper limit of the confidence interval is 5.7 per 10,000.

Let me just add to this answer to question 1.2 that as the question indicated, there certainly was evidence before OCTAVE that those patients at 10 would have had a lower rate of angioedema than 20. Roughly, it appears 1.1 percent as opposed to the 2.4 percent. So, hence the design of the trial to rule out that the rate could be as high as 2 percent, hoping it's around that 1.1 percent, and obviously, disappointingly the rate was at 3.2 percent. So, as you said, Jeff, the answer to 1.2 in that sense is no, although I'd go on and say when one looks at these life-threatening cases, the rate appears to be by estimate 10-fold higher in those in the historical experience who had received 20 as a starting dose.

So, the bottom line is, as I see it, the rates that had been hopefully reduced to levels below the 2 certainly were not. The rate was 3, but it might have that there was systematic under-detection in the previous experience. My own read of this is that there probably is

a dose response, and again the best measure of that would be looking at the fact that we see approximately an estimate of 2 with an upper limit of 5.7 per 100,000 life-threatening cases in the OCTAVE trial in contrast to a 10-fold higher rate than that in the previous experience at 20.

DR. BORER: How about the 1.3? I'm sorry.

DR. FLEMING: I started off by saying the estimate that I accept that was given by the sponsor that the upper limit of the 95 percent confidence interval is 5.7 or about 5 to 6 cases per 10,000.

DR. BORER: Steve.

DR. NISSEN: Well, I think that, of course, Tom is right statistically, but I think there are other factors that we have to think about here. Let me see if I can make this very clear.

I'm concerned that when the drug is administered in the community outside of a setting of a clinical trial, the rigor, the discipline of giving 10 and waiting 2 hours, and then waiting 2 weeks before up-titrating, that we may lose some of that discipline in administration. So, I would tend to raise that estimate somewhat because I'm not convinced that in general use you achieve the discipline that you do in a clinical trial. So, I think I've got to make some upward revision of that

estimate based upon the fact that in clinical use recognition may be a little bit less because people may be further from tertiary care centers, and therefore the risk of a life-threatening event, which is what you're asking us, Bob and Doug, I think could be a lot higher because I don't believe that this plan can be as tight as it was in the clinical trial.

DR. BORER: Blase.

DR. CARABELLO: I see the potential actually for the opposite of that, that in post-marketing that we don't release this to general use. I agree with Steve. I think that's looking for trouble. The risk of an angioplasty is not predicated so much upon the equipment or the atherosclerotic lesion, but rather the judgment of the angioplaster. If you have an experienced person with a lot of judgment, his or her complications are usually less than someone who doesn't do it very well. I think if you limit the use of this to people who have, because of the kind of practice they're engaged in, extraordinary judgment, the complication rate actually could be less.

DR. BORER: Yes. The problem is making that limitation. But let me ask a question and you can comment on that and whatever else, Doug. Dofetalide. In order to use dofetalide, it's necessary to go through an educational program and then be approved for use. So, I guess the

precedent exists. I assume we could do that.

DR. THROCKMORTON: Yes. That's probably not a precedent, unfortunately, that we've had a broad amount of success with. We understand there has been movement towards other pharmaceuticals perhaps in some areas because people have been reluctant to use that.

DR. TEMPLE: But that is because there's an alternative. You can get sotalol without it, unfortunately, for the same use.

DR. THROCKMORTON: Right.

DR. TEMPLE: But here that might not be true.

DR. CARABELLO: But going back to amiodarone or adriamycin, we have plenty of drugs that, even if the agency doesn't restrict them, people restrict their own use because they're scared as hell to use the drugs. A generalist is not going to prescribe adriamycin to the next person who walks into his clinic.

DR. THROCKMORTON: Right, and we of course don't restrict that at all.

And there is precedent for restricted distribution, which is I gather what you're sort of talking about. Normally it's drugs that have extraordinary toxicities that the Office of Drug Safety people are convinced can be managed using those kinds of restricted distributions. But it's very hard. And for an

antihypertensive where we have several dozens of alternatives, it seems like you'd need to be able to make a clear case for doing that. That would be a hard thing, maybe not an impossible thing, but not straightforward.

DR. NISSEN: Just a comment, though. The analogy here of, say, the angioplasty population, Blase, is not in my view a good one, and I'll tell you why. Somebody doing an angioplasty looks at the lesion and all kinds of characteristics and can kind of profile the patient. The problem is other than skin color, I can't look at a patient and know who's going to have it and who's not. So, I could be the world's greatest expert in hypertension, but I'm not sure that I can pick the patient out who's going to have this side effect. So, it's not quite the same as deciding who you're going to put a stint into.

DR. CARABELLO: Yes, but you can, as an expert in hypertension, pick out the group of patients for whom the benefit is the most, at least alter the risk-benefit ratio that way and say, okay, yes, you may get angioedema, but in your case my judgment is you're the patient who's likely to benefit from this drug. People like Dr. Black and others might well want to have this drug in their armamentarium when the other stuff doesn't work.

DR. TEMPLE: We're developing numerous models for risk management. You're familiar with one of them,

bosentan, Tracleer, where there's a central distribution system, and it is shipped directly to the patient from a single place, which allows you to assure that people get the information which could include a video or a lot of different things. That's relatively extreme, manageable with a relatively small population, somewhat intrusive, but in that case we thought it was worth it. And there is a wide range of others. Anne or Julie could probably tell you some of the details.

One that might be considered highly relevant would be what we did with Lotrinex, which has risks of somewhat the same order of magnitude and severity, but we thought it was appropriate for a well-described population of people who were made miserable by their irritable bowel syndrome. That's no so different from people who are put at very high risk because their blood pressure is uncontrollable. So, perhaps a description of that.

But in fact, we'd like to hear what you suggest. Obviously, shipping directly from a central pharmacy is burdensome in one sense but worth it if the risk is bad enough and if you really want to be sure all of the people involved get educated. As an example, if you wanted to be absolutely sure that patients knew what angioedema was like, well, the only way to make really sure is to tell them, enable them to ask questions, show some

pictures of it, or something like that. So, I'm skeptical of whether your local pharmacist will be able to do this in a reliable way, but there might be other people who could do that.

So, there's a very wide range of possibilities. We're happy to hear any suggestions you have, and if that was considered sufficient to make this available, we would work with our own staff and them to figure out what that is. They've ranged from giving good advice, having a patient insert, putting a black boxed warning, all the way to specialized distribution systems.

DR. BORER: Well, that's exactly the point we're up to here, 1.4. I'm sorry. Tom.

DR. FLEMING: I was just going to briefly say, as we're leaving 1.3, I accept Steve's comments as amending my response. My response is based on what this trial shows, and I understand clearly your concern and endorse that concern that this, in fact, in clinical practice could be worse. Blase makes the relevant point that we may well have a differential benefit-to-risk, but other than blacks and smokers we don't know how to prevent this. So, I accept your point, Steve.

DR. BORER: 1.4 requests some opinion about the risk management plan. The sponsor has proposed a risk management plan focusing on patient education by

pharmacists. To what extent can a risk management program based on patient education be expected to reduce the risk of death from angioedema?

Why don't we begin this time with Steve, and then we'll go to Tom.

DR. NISSEN: Well, I think it's a start and I think it certainly does help. The question is how large a magnitude of reduction in risk will we get. It's not going to prevent angioedema. What it might do is get people to seek treatment earlier, and I'm convinced by the arguments from Dr. Kaplan that that could make a difference.

I actually think to really reduce risk, a much more comprehensive program of risk management will be required. I was a little surprised there wasn't much more here for physician education because, in fact, I must tell you that I didn't understand the subtleties of differences in what drugs work and what drugs don't work and so on. So, in my view we would have to get information to most emergency department physicians. We'd have to make sure they understood about omapatrilat, they knew what to do, how to do it, and so on. I didn't see that in here. So, I think the effect here of this is likely to be modest rather than more than that.

DR. BORER: Tom.

DR. PICKERING: Yes, I generally agree. I

think it's a great idea, but my impression is that brief pharmacy education programs are not in general terribly effective. Again, I guess I would be concerned about what happens in a sort of busy pharmacy in Harlem where there's a long line of patients waiting for their prescriptions, how much time there would actually be to do this. I think it's an untested possibility.

DR. BORER: Mike, do you have any thoughts about the education program, the risk management program?

DR. ARTMAN: Yes, I agree with what Tom just said. I think, in a practical sense, it's impossible to say that this is going to be useful or not. It's interesting talking about where the trials were done. I assume if this is going to be used overseas, we heard from Dr. Black how he had an experience in a remote emergency room in Connecticut and everything came out of fine, which he said was like being in Russia. But I wonder what it's really like in Russia. So, I have little confidence that this risk management plan is going to do anything.

Now, that said, the sponsor also sort of made the case that it really doesn't matter because these are obvious signs and symptoms. The patients recognize them. They come on slowly. So, it's six of one, half a dozen of the other. I don't know which side of the fence they're sitting on.

DR. WACLAWSKI: Dr. Borer?

DR. BORER: One second. Once we start this part of the session, we don't really want input unless we ask for it.

Susanna.

DR. CUNNINGHAM: Is there any evidence that actually a pharmacist-based program can do risk reduction? It's a very theoretical thing and I think, really, we've already heard how it probably is quite impractical. So, I would be interested if somebody has evidence that it would work.

DR. BORER: Is there any experience that we can refer to?

DR. TEMPLE: Julie or Anne may want to comment, but I'm sure they'll tell you the answer is probably not. But come on. Don't let me speak for you.

DR. TRONTELLE: I'm Anne Trontelle from the Division of Surveillance Research and Communication Support in the CDER Office of Drug Safety.

We do have some evidence. It's mostly known at this point to be published by Duke Center for Education and Research in Therapeutics on the dofetalide program which involves not only education of pharmacists, but also of practitioners and specially staged introduction of that drug. I think there's some suggestion of improved efficacy

over comparable drugs, but that's again a highly specialized program and one that has probably resulted in substantial voluntary restriction on use of the product perhaps because that program has been perceived to be burdensome. We really are lacking data from any of the other programs at this point.

DR. TEMPLE: But a crucial distinction. You start dofetalide in the hospital or some ambulatory equivalent.

DR. TRONTELLE: That's correct.

DR. TEMPLE: So, it's not your local CVS pharmacist who's responsible for this. It's the hospital pharmacist. Well, no. That was no offense. It's not your local pharmacist. It's a highly specialized group of people and there's a lot of exchange of information. But do we believe that a complicated information system will be handled by local pharmacies? I'm not aware of any information, and as a profound user of many drugs, I think that's very unlikely.

(Laughter.)

DR. TRONTELLE: I think it's hoped for but we don't have data at this point.

DR. TEMPLE: Actually we know that patient package inserts are not well handed out by local pharmacies. That's a not a very hard thing to do. But we

even know that. That seems unlikely.

DR. ARMSTRONG: Maybe I'll speak to that point and also give an opinion on this issue on the table.

There is data in western Canada on pharmacists and cholesterol lowering and adherence to medication which engages pharmacists and actually demonstrates enhanced adherence to the guidelines. So, there is some data.

On the point about the education program on the table, notwithstanding the great intentions and efforts of the sponsor, my worry would be that the infrequency of the event, even with the best efforts of educating the physicians and the patients would lead to desensitization, and I use that term advisedly in relationship to recognition of the event as time elapses.

DR. NISSEN: Would the pharmacist be reimbursed for this activity, or would this be sort of gratis?

DR. THROCKMORTON: Yes. It's important to note and we may want to ask the sponsor to comment on it. The program they've proposed, the outline of the program -- again, remember, the specifics would be worked out were you to give us some level of comfort that it was possible. The program that they've outlined involves a central pharmacist who would interact with the patients initially and I wouldn't want to guess how that person would make their living. The sponsor might want to comment a little. Is

that enough, Elliott, that there's a central pharmacist and then a follow-up with the dispensing pharmacist?

DR. LEVY: Well, there's no intention to make the local pharmacist the focus for patient education. We would use pharmacists in a program that would require that every patient receive counseling before they went to the local pharmacy and got the drug. That, of course, is in addition to physician counseling and to a host of messages that are provided them through the packaging and educational materials.

DR. CARABELLO: I personally don't think we'll have too much success in mitigating risk, although patient education to let them know what angioedema is would clearly be valuable. Going back to my original plan, I think our best bet is trying to improve the risk-benefit ratio by focusing on the prescriber so that whatever the risk is it's only matched by the higher benefit by prescribing this to some specific patients.

Finally, I'd like to distance myself from any group that would compare both South Dakota and Connecticut to Russia. I think that's a very dangerous thing to do.

DR. BORER: Because you have asked for a lot of opinions about this, I want to say a couple of things here in addition to what's already been said.

My perception of the risk has been modified in

an important way by Dr. Kaplan's comments and the fact that there are perhaps several hours off usually before major sequelae of angioedema might be expected to occur. On the other hand, that means you have to be within a couple of hours of help and you have to be aware that you need help.

I share the concern that has been raised by a couple of people on the committee that a patient education program just isn't going to cut it, or by itself it won't. It's an important component if one could do this at all, but the physician education is crucial. I don't know how one could achieve adequate physician education without limited distribution, which is a tall order, as we've heard. So, I have real concern that a practical program could be developed.

But I do not believe that a risk management plan focusing on the patients and the pharmacists would be sufficient to deal with the risk if we perceived the risk to be an important risk relative to the benefit and if -- on and on and on. Again, I think we still have to discuss what the risk is in view of the information we received today, but I don't think this kind of a plan would do it.

Was there another comment?

DR. THROCKMORTON: Susanna, do you have a comment at all?

DR. CUNNINGHAM: No.

DR. BORER: Tom, I'm sorry. I didn't ask you specifically for a comment about this.

The sponsor has shown the results of OVERTURE --

DR. TEMPLE: Jeffrey, before we leave that, could we hear other people's views of that last point? I mean, that's not unimportant, after all. You are skeptical that anything but a limited distribution system which allows you to interact clearly with the physician -- I assume that's the point --

DR. BORER: That's right.

DR. TEMPLE: -- is likely to do anything. Is that everybody's view? That's potentially very critical depending on your answer to the rest of it.

DR. BORER: Well, let's hear.

DR. NISSEN: I also concur.

DR. CARABELLO: I think I made my own point clear.

DR. CUNNINGHAM: I agree.

DR. ARTMAN: Well, I agree but yet even that -- there are two issues. One is controlling the use of the drug and restricting its use, and the other is managing this adverse event and that we can't really predict who's going to get that. There are some that are at little bit higher risk than others, but anybody who's on this drug for

any given time at any dosage may develop significant angioedema. So, yes, I agree with that that you can maybe minimize it by minimizing the number of people you expose, but I think it's a whole different issue to say that that's going to reduce the risk. I don't think it will.

DR. TEMPLE: The theory I think -- Blase has said this several times -- is that you make the risk acceptable because the benefit is particularly good. That's certainly the theory of Lotrinex. If you only give it to people who are willing to accept and understand all the various risks, then the benefits might outweigh the risk for that portion of the population, whereas if you just gave it to everybody with IBS, you wouldn't feel that.

DR. ARTMAN: Well, let's extend that logic that Blase used to amiodarone and angioplasty. There are knuckleheads out there using amiodarone and angioplasty. And some of these things started out being sort of restricted. So, once the cat is out of the bag, all bets are off.

DR. NISSEN: There's one other part of the equation again I think that's very important to understand, and that is that the suggestion here is that we can optimize risk-to-benefit ratio by selecting patients that are most likely to benefit. Tom Fleming tried to drill down very hard to find that group that's most likely to

benefit and to see whether or not there's very good evidence here that lets us identify such a group and then to estimate the magnitude of benefit.

The problem I have is I'm not quite sure how to drill down to that group that's most likely to benefit, and I'm certainly not sure how to estimate the magnitude of benefit of a 3 over 2 millimeter blood pressure difference in a new class of drugs. So, this is all predicated on the assumption that we know that and therefore, by picking these high risk individuals, we can somehow optimize overall benefit, and I just don't think the data gives us that information.

DR. BORER: Let's go on to question 2. The sponsor has shown the results of OVERTURE, a comparison of omapatrilat and enalapril in the treatment of chronic heart failure. If the results of this study are as presented, how relevant are these data to the approval of omapatrilat for hypertension?

Tom and then Steve.

DR. PICKERING: Well, I certainly think the results are relevant because I guess we were hoping there was some evidence of additional benefit on outcomes from omapatrilat above those of enalapril. But my own interpretation is that the study was negative. In terms of the blood pressure reduction, there doesn't seem to be any

convincing evidence that there was a difference using the b.i.d. dose. On the other hand, I guess you could argue that the doses weren't necessarily the maximal that are used for blood pressure control, and it wasn't designed as a blood pressure study. So, the bottom line is I don't think it adds a whole lot of support for the case.

DR. BORER: Go on to 2.2. How reassuring are these data with respect to the use of omapatrilat in a hypertensive population? I think you've just answered that, but do you want to elaborate a little bit? I think you've answered it.

DR. PICKERING: Yes.

DR. BORER: Steve.

DR. NISSEN: I guess I think the OVERTURE data are minimally relevant. I'm glad we have them, and I agree with Milt Packer's suggestion that it does tend to make us believe that there's not being harm done by this drug with respect to that particular group of patients. But because it is a different group of patients, it's hard to interpret it.

I think I'm convinced that probably there was a blood pressure difference in OVERTURE, particularly given the greater incidence of hypotension. But I think the amount of weight I would put on OVERTURE in our decision is very, very small, and I wouldn't urge us to consider it

very much in our overall decision making.

DR. TEMPLE: Let me ask a specific question. You've raised the issue several times now that you don't know what a new drug that hasn't got outcome data does. You don't know whether the expected benefit of a 3 millimeter of mercury systolic pressure difference -- okay.

Well, there are a number of possible reasons for that, but one of them is maybe it's like a high-dose diuretic and it kills you in some way.

One might have argued -- I'm not trying to put words, but we need to understand this because, without understanding, we might go off and say the wrong thing. One might think that OVERTURE is somewhat reassuring on that point. You have a fragile population susceptible to getting MI, sudden death, all those things, and that didn't happen to them. So, why doesn't that, to some extent, contribute to your answer on that?

DR. BORER: Let me respond to that. It does for me. I don't think that the OVERTURE data are the panacea to respond to our concerns, but it's hard not to begin to develop the belief that there isn't a smoking gun in terms of other cardiovascular toxicity out there. When you look at the OVERTURE data, as Tom said, it's not an antihypertensive study and the doses were half the maximal doses that were given in OCTAVE and half the maximal doses

that would be used in clinical practice, though they were relevant for a heart failure study. But remember, of the people with heart failure, more than half had coronary disease as the basis, and we didn't see a jump in myocardial infarction, sudden death, and whatever.

So, I think these are useful data. They're not dispositive, but I think they're useful data in making us focus in on the safety concern that we have to balance against the benefits, specifically the angioedema. It wipes away some of the potential peripheral noise.

DR. NISSEN: Bob, I wanted to also respond directly. Let me see if I can be clear about this.

I agree with Jeffrey and I agree with Milton that it does, in fact, help us in the belief that there is no harm being done by the drug. But I was speaking to the question of what inference can we place on that 3 over 2 millimeter blood pressure decrease upon the likelihood that that will produce an incremental benefit on events, and I can't tease that out of OVERTURE. I still don't know yet whether the better blood pressure reduction that we get with omapatrilat will, in fact, ultimately translate into a reduction of events.

DR. TEMPLE: You obviously have no direct information on that. And Henry may be invited to talk to this too. The people who do meta-analyses and look at

various drugs generally reached the conclusion that, if you like, it's the blood pressure, stupid, and that a fallen blood pressure, unless it's balanced by something toxic or some failure to treat a component, maybe like doxazocin, will have the expected effect. That's not proof, but I'm curious to know where your skepticism comes from. Do you doubt that or where does it come from?

DR. NISSEN: I do doubt it, and I doubt it because of some studies. I doubt it because LIFE is a study where similar blood pressure reductions produced different effects on events. Looking at all the different events, I'm pretty well convinced, for example, that the same amount of blood pressure lowering with a calcium channel blocker may lower stroke to a greater extent than, say, ACE inhibitors, whereas lowering with ACE inhibitors may do a better job of preventing heart failure. I think there are lots of clinical trial data that suggest it is not just the blood pressure, stupid.

I think that given that fact and given the fact that we've got an entirely new drug in a new class, I cannot estimate -- and OVERTURE doesn't allow me to estimate -- the magnitude of benefit of a 3 over 2 blood pressure increase on the long-term morbidity and mortality in this population. It was even a different population from OVERTURE.

DR. BORER: Are there any other comments from the committee about OVERTURE? Susanna. I'm sorry. Tom.

DR. FLEMING: I find OVERTURE very relevant to the setting in which it was conducted. In this chronic heart failure setting, we see a 6 percent reduction in these primary endpoints, and in my sense, a nonsignificant modest difference here is not an adequate difference when you're looking at angioedema risks as part of the overall spectrum of side effects.

To get to the question, though, how relevant is this to the antihypertensive setting? As I understand it, in essence the way it's supposed to be relevant is we -- and I'm going to oversimplify the world probably, but omapatrilat, let's say, is an inhibitor of ACE and NEP, and let's say that it's the inhibition of NEP that's the causal mechanism by which we're achieving a higher level of blood pressure control. So, what I really want to do is be able to be reassured that the only effect that that inhibition of NEP has is mediated through this blood pressure control. That's essentially, I assume, the reassurance I'm supposed to get out of this study. And yet, I don't see the magnitude of blood pressure difference in this setting that I have in the antihypertensive setting.

I struggle to see the logic behind how I'm going to be able to then use this as a way to conclude that

in the antihypertensive setting, that these data provide me compelling evidence or reliable or even useful insights that I'm not going to have unintended effects on clinical endpoints which, in fact, wouldn't have to occur in the magnitude that they would occur in a chronic heart failure setting to be important on relative risk. Events are much more rare in an antihypertensive setting. So, if something doesn't show up in a setting where events are frequent, it doesn't mean that there isn't a signal there that's being lost in the background of a lot of other naturally occurring events that in the antihypertensive setting would be important. So, I don't see how this is informative for our setting.

DR. BORER: May I just ask you to elaborate a little further, Tom? I wonder whether the data from OVERTURE have to be understood in context of the data from OCTAVE about cardiovascular events. There was no significant reduction in cardiovascular events, but they went in the right direction and we didn't see a problem with excessive cardiovascular events in this very high risk population of OVERTURE. Taken together, do they or do they not give you some confidence that we don't have to be overly concerned?

DR. FLEMING: There's not nearly enough known to draw that conclusion. One could argue -- and maybe it's

entirely wrong -- that what small trends that are there are, in fact, due to the intended mechanism that is the added blood pressure control.

What I want to be reassured about is the point Steve has articulated on several occasions, and that is if we now have a new agent that not only is an inhibitor of ACE but NEP and it may be through that mechanism that we get this additional 3 millimeter blood pressure control, that I can now conclude I'm going to achieve the full benefit in reduction of clinical events, and there won't be any other unintended effects on cardiovascular events. I can't glean that from the OVERTURE data.

DR. TEMPLE: But, Jeff, this is really critical. If the committee as a whole doesn't believe that lowering the blood pressure more, even if that were well documented, is of any value, then we can stop now.

DR. BORER: But I'm not sure we're at that point.

DR. FLEMING: We're not at that point.

DR. BORER: We'll answer that question.

Blase.

DR. CARABELLO: Just to make the point that in OVERTURE, I think it is somewhat reassuring that in what is surely a very sick group of patients, we didn't see increased cardiovascular events.

But the other point I was going to make is that in some respects this is comparing apples with freight trains. Remember, cardiologists only have to remember two things at once. In this case it's total peripheral resistance and cardiac output. And the two things supporting blood pressure and heart failure are so vastly different with every system known to man revved up and screaming at one another. Whatever the difference between that is and in essential hypertension I don't know, but I suspect that we're talking about two very different pathophysiologic settings.

DR. BORER: Paul.

DR. ARMSTRONG: Just to respond to Bob's point, I'm not sure that the prevention of the degradation of AMP, adrenomedullin, and bradykinin long term aren't harmful. So, I'm not prepared to accept blood pressure lowering with this agent as a likely mechanism for the prevention of long-term cardiovascular morbidity and mortality.

DR. BORER: Bob, has pointed out that we do have to deal with this issue as to whether we accept blood pressure lowering as a surrogate. I think that what's developing from this discussion may not be that everybody wants to tell the FDA to junk the surrogate -- or maybe they do and we'll ask specifically -- but that when the surrogate is achieved by the use of a new agent that acts

by a different mechanism, are the risks associated with the use of that new agent sufficiently modest so that even though there may be mechanism-specific differences in the magnitude of benefit from a given degree of blood pressure lowering, we can assume that the blood pressure lowering causes a benefit sufficient to overcome those risks that we don't understand so well. That's sort of a complicated statement, but I think you get the idea.

DR. TEMPLE: But it is fundamentally untestable. You can't use this in a 10,000-patient study because it wouldn't be even ethical to even give those people the drug.

DR. BORER: Right.

DR. TEMPLE: Just remember.

DR. BORER: Just to answer your question, is there anyone here at the table who wants to tell the FDA today that we just cannot accept the blood pressure lowering as a surrogate anymore?

DR. THROCKMORTON: In this case, you must say -- since yesterday you said you could do that for drugs within the same class. Specifically you must now be saying comparing drugs not within the same class.

DR. FLEMING: Jeff, we don't really want to make a blanket statement. Right? I mean, I think as has been articulated by many people, it depends on the

circumstance. There are an awful lot of surrogates that I wouldn't put much stock in at all. This one is one that stands out among the few that really has some considerable credibility, and yet you don't blanketly apply it. And there are certain settings, for example, within drugs within the same class where there are no detected concerns in safety where you're going to be more confident in relying upon it than in other settings where you have different drugs in different classes or, in particular, as is in this case -- I'm not saying you wouldn't give it some credence, but there is a higher bar that you have to hit when you have to overcome an important significant side effect.

DR. BORER: I think that that statement probably stands for the committee here. The committee isn't suggesting that the surrogate has to be scrapped. We don't have the database to be able to suggest such a thing. But with this particular agent, there is information that indicates a risk that's higher than we might have expected for some new antihypertensive drug, and now we have to explore whether the risk or other risks that we haven't quite fully fathomed yet outweigh the putative benefits of the blood pressure lowering. And that's what we're sort of grappling with here.

DR. TEMPLE: I think I'm hearing that you think

under these circumstances, it's sufficiently uncertain as to whether there is a benefit, that there cannot be anything that outweighs the well-known risk. The risk is documented. That can't go away. You can manage it, but you can't make it go away. But in this case, you can't know with enough certainty that there's a benefit of a 3 millimeter of mercury difference, so that there is really no presumed benefit from that outcome.

DR. BORER: I don't think that's the consensus here yet.

DR. TEMPLE: I'm being provocative. I want to hear what you do think.

DR. NISSEN: I know you are and I really want to try to directly answer that a little bit.

The reason that I think Tom Fleming said that it depends is because it depends on the magnitude of the difference in blood pressure and the magnitude of the risk. So, if you give me a drug that has no defined risks above that of comparators and has a fairly robust and substantial blood pressure advantage over a 24-hour period of time, we're going to probably be just fine. And we did that yesterday. We took a few hundred patient trials, a couple of trials, and we said a drug in the same class with no special risks that has a couple of millimeters better blood pressure reduction is superior.

So, if this drug could produce an 8 or 10 millimeter increase, very, very robust differences, that would shift the equation a little bit. And if the risks here were a bit smaller, if it were only a twofold increase in the risk of angioedema, not a threefold, and there weren't these racial issues.

And so, the reason it's context that makes a difference here is we have to as clinicians and you have to as an agency balance the magnitude of the benefit with the magnitude of the risk. What I think we're saying is that for a 3 millimeter over 2 millimeter blood pressure difference, we know that there are interclass differences in effect on events, and those could potentially overwhelm that 3 over 2 benefit, particularly in the context where safety is a problem.

DR. TEMPLE: I just want to ask one other thing. To my best knowledge, no placebo-controlled trial of any class of drugs, which includes calcium channel blockers, reserpine, hydralazine, even high-dose diuretics which are lethal, has failed to show a favorable effect on stroke in other matters. That doesn't mean there can't be differences between the classes. There can.

But I would have said the general observation of lowering blood pressure, barring some bizarre thing like causing arrhythmias, is always good for you was fairly well

established. You're absolutely right. That doesn't mean there can't be interclass differences. But you don't think that's necessarily good enough because you can't really quantify it.

DR. NISSEN: Well, it's true, true, and unrelated. I mean, the fact that drug X is better than placebo, because it lowers blood pressure, isn't the same as saying that drug X is better than drug Y because it lowers blood pressure by a little bit more. I think that's the problem. The problem is we have shown interclass differences. So, it's true that every drug that lowers blood pressure has been better than placebo. I think that's right.

DR. TEMPLE: So, across class, even something that was a little bit better at lowering blood pressure might not be better because of other factors.

DR. NISSEN: And that's what ALLHAT is testing in an enormous population. If ALLHAT is a wash, then okay. But I would make you a prediction that different endpoints in ALLHAT may go in different directions based upon which agent you use independent of blood pressure.

DR. BORER: Today, however, we have to make our judgment based on what we know. Of course, ALLHAT isn't available yet.

And I want to hear Tom's comment about this,

but I think to put it in a slightly different context, I'm willing to accept that 3 over 2 is good. If omapatrilat is what it takes to get there, that's a good thing. The issue is do the benefits outweigh the putative risks. At the end of the day, we're going to have to come to a qualitative judgment of that because there is absolutely no way we can quantify these things. And we're going to get there, I promise. I don't know what that judgment will be, but that's what we're going to have to do and that's what we're sort of moving towards.

Tom.

DR. PICKERING: Yes. I'm one of those who says that a 3 over 2 reduction in blood pressure is extremely important clinically for the reduction of risk.

I'd like to sort of clarify what we're talking about in terms of risk here. Maybe angioedema is one that's clearly defined, but I think I'm sort of hearing insinuations that there may be other risks that we really don't know about, and if so, I think that's unfair to the sponsors. What we should be judging is the blood pressure and the known risks at this stage.

DR. BORER: Yes, I agree with that statement to the extent that we have looked at the adverse event profile for this 25,000-patient study plus the OVERTURE data for a different population. That's true. If anything, it would

tend to reassure one that bad things aren't happening. I think Tom's point, which is absolutely right, is it also doesn't tell you you're clearly benefiting in terms of event reduction from the blood pressure lowering. On the other hand, that's not what the trial was designed to do, but it does make a pretty reasonable case that there's not a smoking gun out there that some horrible thing is going to happen besides the angioedema, the relative importance of which we're going to have to judge at the end of the day.

Why don't we try. Unless anybody has anything else to say about 2, we'll move on to 3, which is fairly specific. Consider the antihypertensive effects of omapatrilat relative to other drugs. 3.1. Is omapatrilat superior to enalapril? What results support this?

Tom, can you give us an opinion about that?

DR. PICKERING: Yes. I would say the answer is yes and I accept that these studies against twice-daily enalapril might have reduced the superiority a little, but I would expect it would still be there.

As I said earlier, I'm sort of disappointed that there aren't head-to-head studies between omapatrilat and enalapril or lisinopril plus a diuretic. I would very much like to see what those data would show. I know there's an additive effect when you add omapatrilat to a

diuretic, but I think the head-to-head studies would have still been helpful.

DR. BORER: Steve, what do you think about omapatrilat versus enalapril?

DR. NISSEN: I'm convinced. If you show it in a 25,000-patient trial of this strength, the evidence is just overwhelming that it is superior at lowering blood pressure to enalapril. Not controversial.

DR. BORER: Tom, do you have any concerns about that? No. Anybody else?

(No response.)

DR. BORER: So, we're willing to accept the answer to 3.1 as being yes.

How about 3.2? Steve, why don't you start.

DR. NISSEN: Two adequately controlled trials against lisinopril in reviewing Dr. Throckmorton's material -- and I think they were well done, and there's also ambulatory blood pressure data. So, I think that in fact there is adequate evidence of superiority to lisinopril.

DR. BORER: Tom.

DR. PICKERING: I agree.

DR. FLEMING: Well, I just have a comment, additional thought that will apply to 3.2, 3.3, and 3.4, and that is I certainly agree the data are there to establish a superior antihypertensive effect. All of these

studies, though, that will be relevant for 3.2, 3.3, and 3.4 had starting doses of 20. So, these superior antihypertensive effects were established in settings where, from a point estimate perspective, the angioedema rates were maybe an order of magnitude higher than what we see in OCTAVE, although I suppose it could reasonably be presumed that had these studies also been done with the lower starting dose, that they still would have yielded comparable improvements in antihypertensive control or effects.

DR. BORER: So, you've extended now to 3.3 and 3.4 and accepted omapatrilat as superior to the other drugs as well.

Tom Pickering, would you agree with that?

DR. PICKERING: Yes.

DR. BORER: And Steve?

DR. NISSEN: I do not. I reviewed this pretty carefully. Let's take 3.3 first. There were two trials against amlodipine, one of which was positive with a delta of minus 2.1, and one of which showed a delta of minus .3 and a p value of .6. So, if you say it takes two trials, the two trial rule was not achieved against amlodipine. Now, both trials were adequately done, but I don't think there are two positive trials. Doug, correct me if I'm wrong, but when I read your review here, the study CV137-

032, your review said, failed to detect a significant difference between omapatrilat and amlodipine, and the delta was minus 0.3, p equals .617. So, I would say not proven.

And for 3.4, I don't think there's adequate data against losartan. I think the two trial rule requiring well-performed trials simply isn't there. But correct me if I'm wrong, Doug. You've reviewed this.

DR. THROCKMORTON: Review the losartan data, maybe.

DR. NISSEN: You'll have to point me to the --

DR. BORER: While you're looking for --

DR. NISSEN: I think the only trial I saw was the LVH study, but maybe there's something I don't know about. I don't think that was adequate.

DR. BORER: While you're looking for them, though, remember that the replicability of effect principle is really an approvability principle. We're talking here about whether we have data that would convince us rather that for approval purposes for moving forward with an opinion about whether this drug adds something that the drug actually was more effective than losartan or amlodipine, in which case it might be reasonable. I'm not suggesting you should do it, but it might be reasonable to add the data together and look at the average. Both trials

went the same way, for example. I'm not suggesting that that should be the opinion, but one might look at it that way.

DR. NISSEN: Let me tell you why it's relevant.

DR. THROCKMORTON: Let's ask the sponsor to just briefly review the losartan.

But just to comment, the general notion here was, is there any superiority that you discerned for any comparative antihypertensives? Where you define none, then we're done.

DR. LEVY: Just two points. First of all, in addition to the 38 study, there were two adequate and well-controlled trials versus losartan, one of which is shown here and the second of which is shown on the next slide, which was an ambulatory blood pressure comparison shown on the right.

I'd just like to briefly comment on the -32 study. Dr. Throckmorton's comment on the office trough diastolic blood pressure results are correct. This was an ambulatory blood pressure study, powered for ambulatory blood pressure. Primary outcome measure, ambulatory mean blood pressure, which was positive, as were ambulatory systolic, diastolic, and office systolic pressures. The sole outcome measure in the entire program that I described to you that was not positive was the office diastolic blood

pressure in this study which was not even a primary outcome variable.

DR. NISSEN: That's helpful I think. That might have been pruned, Doug, from your packet because in the material we got, the losartan studies were not in here. So, I didn't get a chance to review them.

DR. THROCKMORTON: No. That's correct. They were not part of my original review.

DR. NISSEN: So, when I said there wasn't adequate evidence, it was based upon what I was given to review. So, I stand corrected. It sounds like you've done the two adequate trials against losartan. So, I think the answer to that is yes.

DR. THROCKMORTON: Jeff, we've heard what we need, I believe, on this question. You've identified agents where superiority is adequately demonstrated. That allows you to go the next step I think.

DR. BORER: Which we will now do. Question number 4. And here we're going to need a vote. With what potential benefit should the risk of angioedema be balanced? We may need a little clarification here from the FDA, but let me read through the question. The sense of it is reasonably clear, but we may need some specific clarification so we answer you correctly.

With what potential benefit should the risk of

angioedema be balanced? OCTAVE allowed the addition of no new antihypertensive drugs during the first 8 weeks, at which time the blood pressure was about 3 over 2 millimeters of mercury lower on omapatrilat. During the following 16 weeks, other drugs were to be added to meet blood pressure goals, but at the end of 24 weeks, the blood pressure difference was still 3 over 2 millimeters of mercury. What explains the persistence of the differential effect at 24 weeks?

4.1. Is a regimen including omapatrilat able to lower blood pressure to an extent that combinations of enalapril and other drugs cannot? Which is one of our key issues here. If so, is the risk-benefit comparison between the risk of angioedema and the expected reduction in cardiovascular events attributable to this blood pressure difference?

DR. TEMPLE: I think the question is should the risk-benefit comparison be based on that difference. That's sort of the question that Norm emphasized in his review and that I raised before. What if they had added another drug or gone up in dose, which didn't happen? So, that's the question.

DR. FLEMING: Which the second part of the question does more get at.

DR. THROCKMORTON: That is the second option.

The first option, to phrase it another way, is that omapatrilat has a property that allows a regimen using it to lower blood pressure 3 millimeters of mercury more than any regimen containing enalapril by some means. Even if you add additional medications, you can't obtain those additional 3. If so and you concluded that 3 millimeters of mercury matter, then it seems that what you want to know is the potential benefits of those extra 3 millimeters of mercury compared versus the risks of angioedema.

If, on the other hand, you're not convinced or on the other side, that you believe that perhaps just adding one more drug in the OCTAVE trial would have sufficed to bring the enalapril group to the same blood pressure control as the omapatrilat group, then perhaps -- and that's what we need to have some discussion about -- the comparison is the risk of adding that additional approved medication compared with the risk of the angioedema.

Does that help to clarify things?

DR. TEMPLE: But also, you don't know what would have happened had they done that because it didn't happen.

DR. THROCKMORTON: They may be convinced that they do.

DR. TEMPLE: Yes, okay.

DR. BORER: I'll tell you what let's do here because you said you wanted a specific vote on the components of this and we'll restructure it so you get one. Let me start by asking Tom for his opinion because he can't vote, and then we'll move on from there.

DR. PICKERING: My problem with this question is that I don't think this was a question that OCTAVE was really designed to answer. It was designed to look at the relative incidence of angioedema. The word is "cannot." I'm not convinced that if the study had continued longer and additional drugs had been added to the enalapril group that the difference might have become smaller. I don't think I know. It may have persisted, but as I say, it wasn't really designed to get at this question.

DR. BORER: Steve.

DR. NISSEN: My sense here is that this was an artifact of the trial design, and let me see if I can be clear. There were only two opportunities for dose titration in the trial, in a relatively short-term trial. If you think about patients and physicians and how they care for them, there's a little bit of inertia here, and if you see a patient over time and your blood pressure is not falling, eventually you come around to adding another agent. Now, should we be quicker on the draw? Maybe. Are we a little lackadaisical? I think Henry and others have

taught us that we are.

But my guess is that the reason there was such a small amount of additional drug use in the enalapril arm related to that artifact of only having two opportunities to do so, and if you had carried this trial out for a year and had five or six or seven attempts, or opportunities rather, to add additional drugs, that eventually you would have seen some upward creep in the additional drug use in the enalapril arm and that would have equalized. We don't know that. I'm just trying to help explain why that difference persisted.

DR. TEMPLE: Some trials, of course, insist that you titrate and insist that you add if a criterion isn't met. This didn't do that.

DR. NISSEN: That's right.

DR. TEMPLE: The question is how important it is.

DR. NISSEN: Yes, and I guess what I'm saying is I think this was a design issue, not an efficacy advantage because I'm convinced that if those physicians had been instructed to do so and given time to do so, they would have closed the gap between the two regimens. Or they might have.

DR. CARABELLO: But, Steve, why wouldn't it work with the other arm as well?

DR. NISSEN: I'm not sure I understand your question.

DR. CARABELLO: Well, why wouldn't the ability to titrate omapatrilat more aggressively continue to maintain the gap? Why would they only titer to one of the arms?

DR. NISSEN: Well, because there was a differential. So, the group that's in the differential with the higher blood pressures is going to naturally get more adjunctive therapy. I think that there's a tendency. If you're treating to target and you give the same target to both arms and one arm has omapatrilat, then the group that doesn't have omapatrilat is going to end up getting more adjunctive therapy and is going to tend to close that gap. So, I'm going to guess that a 1-year trial with five or six opportunities to titrate would have -- now, whether it would have closed it completely or not, nobody knows because it wasn't done. But I think that's the explanation for the difference.

DR. BORER: Yes, I think an important issue here is that, for better or for worse, we treat to goal and once you achieve the goal, perhaps inappropriately there really isn't an aggressive attempt to lower further. If you weren't able to achieve the goal in either arm, presumably you'd give more and more and more drug until you

did, and then we would have known the true impact of omapatrilat.

Susanna, do you want to talk about 4.1 and 4.2?

DR. CUNNINGHAM: Well, I don't think I know for sure what would have happened, just as Steve has just outlined. So, I think it's unfortunate.

DR. BORER: Do you have any other comment?

DR. CARABELLO: No.

DR. BORER: Mike, Tom.

DR. FLEMING: Should we be answering both questions?

DR. BORER: Yes.

DR. FLEMING: Actually there are two parts, as I see it, to 4.1. The first is relating to the answer that Steve was just giving about whether omapatrilat is able to achieve better blood pressure lowering than other combinations would be able to do. I support Steve's answer and I would ask one other scenario that could justify why more aggressive dosing might have closed the gap is that if a lot of patients at baseline that we've had reported to us had been on ACE inhibitors and had not, in fact, achieved adequate response, if I'm going to randomize those people to something else to achieve a better result, omapatrilat is a very logical option as something that provides a more aggressive approach. If I'm going to randomize in control

to enalapril, one of the ways that you could have gotten better response there would have been a b.i.d. or more aggressive dosing in that as a control arm.

What I don't know -- and I've already said I won't put too much stock in the OVERTURE trial, but maybe the OVERTURE didn't show as much difference in blood pressure dosing because of that reason. It's uncertain, and I would agree with Tom's original answer. I think the trial was not designed in a way to truly address this question. It may not be true and it may be true that more aggressive dosing with enalapril and then with other adjunctive therapies might, in fact, have closed the gap.

The second part, as I understand the rewording of question 4.1 in the second part, it's -- and I'm going to read it as I understand the rewording -- what is the risk-benefit comparison between the risk of angioedema and the expected reduction in cardiovascular events? At least I'm going to answer the question as I've just worded it.

The risk of angioedema at the most serious level, as has been approximated here, the upper limit of the confidence interval is around 5.7 per 10,000, although it could be considerably larger if one, in fact, starts with a dose of 20.

What is in fact the benefit? And there are two ways of getting at the benefit. One way is through the

surrogate and extrapolating from a 3 millimeter reduction in blood pressure and essentially using estimates from HOPE and other sources that would say we would expect per 1,000 person-years 30 clinical events of cardiovascular death, MI, heart failure, stroke, and using the HOPE trial with the 3 millimeter reduction, maybe a 15 to 20 percent relative risk reduction, that would translate to something on the order of 40 to 80 events per 10,000 person-years.

We actually observed much less than that. Granted, the data are limited, but we still had 170 events, and these are from the very trial on which we're trying to make our assessment. The actual event rate was maybe half what was expected, and in turn, the actual relative reduction was half of what was expected. So, we ended up with maybe a quarter of the number of reduced events. The data of 89 versus 82 cardiovascular deaths, MI, heart failure, stroke at 6 months translates into roughly 10 to 15 events prevented per 10,000 person-years.

So, I stand back and basically make the assessment of what's prevented based on two sources of information, one, what the data actually said, and that's 10 to 15 percent, against what you might extrapolate if you truly believed in the surrogate. And it's probably twice that size. So, that's what we achieve in the context of what we are seeing as serious events of life-threatening

events of angioedema which are roughly 5.7.

What it indicates to me is that there is a favorable benefit to risk in those analyses, although the serious events of angioedema are not trivial in the context of what we're trying to achieve, hence the concern that can we achieve what we're trying to achieve in ways without raising those events.

DR. BORER: Paul.

DR. ARMSTRONG: I would say that based on the doses of amlodipine and diuretic we heard were used in the adjunctive therapy, that there was additional opportunity for enhanced blood pressure control in the comparator arm.

I would say in relationship to 4.2 that the obvious blood pressure lowering superiority of the new agent may translate into a long-term benefit, and if the risk of angioedema was not a player, I would be comfortable in that proposition.

But given that there are three separate neurohumors that are affected by this agent and at least one and perhaps others that we don't know about is modulating the angioedema, and that the risk of angioedema is not likely to diminish over the lifetime of a hypertensive patient once the early first or 2 days is obviated, I have meaningful and real concerns.

DR. BORER: Bob and then Doug.

DR. TEMPLE: I just want to be sure we separate the two things out. The first part of the question is about do you believe this difference would persist if people had titrated or added other drugs, and what I heard from a number of people is the study wasn't designed to tell that, therefore you can't know in a hands-on way. You might suspect, but you can't know.

And the second was Tom's observation that even though there was a better control of blood pressure, you didn't the events. But I have a question for you on that. This was a relatively short-term study. Is that a question that could be answered in a study of this duration, or does it really take a little longer before you even have a shot at showing a benefit from that change? So, that's a question of how negative the failing to find that difference is.

DR. FLEMING: If what you're saying is we can estimate a relative risk reduction in these clinical events, but recognizing this is a small study, how wide is the confidence interval?

DR. TEMPLE: No. I'm saying it's short. It's true the benefits of antihypertensive therapy are observed relatively quickly, but I don't think they're usually seen in 6 months or a year very prominently. So, I'm not sure what the expected benefit would be even if it had the usual

effect. So, I'm really asking how negative should one feel about the failure to see the reduction in actual risk in that study. Obviously, my implication is I'm not sure you would have expected it in a study of that duration.

DR. BORER: I'd like to provide a response. Everybody else has responded to this. I look at it just a little bit differently than some of the other commenters. And I'm going to divide it into parts here if I can.

Is a regimen including omapatrilat able to lower blood pressure to an extent that combinations of enalapril and other drugs cannot? I believe that it can, and the reason I do is not that there are direct data. There are not direct data of the kind that I would have liked to see to come to a firm conclusion. But in every comparison that we saw, regimens containing omapatrilat were better than the comparators. So, I believe that a regimen containing omapatrilat would be able to lower blood pressure to an extent that combinations of enalapril and other drugs cannot.

However, I'm not sure what group of patients that's referable to because that study wasn't done. The truly refractory patients weren't identified here. So, if you asked me to write a label, I would be hard-put to do it because I'm not entirely sure what group we're talking about, and I'd like a little bit more evidence that in such

a group, this drug actually does provide a benefit of the magnitude we're talking about, though I believe it probably does.

But having said that, I believe that the judgment should be based on the risk-benefit comparison to angioedema because I haven't seen evidence that there is any other meaningful risk that we ought to be worried about. There don't seem to be other problems coming up with this drug.

Having said that, if I accept the 3 over 2 millimeter fall in blood pressure, additional reduction in blood pressure, if I accept that, in a truly refractory group that I didn't really look at here, but if I accept that for the moment as the benefit, or the surrogate for the benefit, and I compare the angioedema risk, I would come to the same conclusion that I think Tom did, that the benefit outweighs the risk.

Why do I say that? It's not just on a basis of event rate, but the fact that the risk of angioedema is not immediate closure of the airway and sudden death, but that in most cases the problem is not so severe as that, that there's some time to respond, and on and on and on. So, the really meaningful mortal risk is I think relatively low although we probably underestimated it here because of the fact that this was a study constructed as it was.

But my real sticking point here is figuring out who these people are that the drug would be used for, how you would define that. I'm saying it's people who were refractory, but I'm not sure exactly how I would define that.

Then the issue of the persistence of the blood pressure difference at 24 weeks. Is it a consequence of trial design goal, the blood pressure goal or the goal blood pressure, inadequate use of additional drugs? I think it's all of the above.

DR. THROCKMORTON: But you just said that you believed in your heart of hearts that despite difficulties in interpreting the 24-week data, that there was some population there for which omapatrilat alone had a greater blood pressure lowering effect than combinations of enalapril and other agents?

DR. BORER: No, no. That a regimen including omapatrilat would achieve better blood pressure control than a regimen of multiple drugs that didn't include omapatrilat.

DR. THROCKMORTON: I think we're saying the same thing, that you couldn't get to the place that you could get with a regimen containing omapatrilat with a regimen --

DR. BORER: Without it.

DR. THROCKMORTON: -- without. Then your trouble is you're not sure you can identify the population, but that the data from that trial are sufficient for you to believe that.

DR. BORER: Well, no. I said the data really are not sufficient. I'm making an inference. I'm making a leap of faith here.

DR. THROCKMORTON: I want to understand that leap.

DR. BORER: I'm looking at the data here and I'm saying in every comparison that was made, omapatrilat was superior to the comparator. Within the OCTAVE trial, there were, I believe, undoubtedly people who would be within the population for whom the sponsor is suggesting the drug should be used, people who were on multiple drugs probably at reasonable doses who just didn't respond and who were given omapatrilat instead of enalapril as part of the regimen and who did better.

It's just that I haven't seen precisely those data. The sponsor may be able to tease them out. I don't know if the documentation is sufficient to do that, but certainly one could look at the subpopulation that was on multiple drugs at at least such and such a dose of each of the components and omapatrilat rather than enalapril and could show that that group had a greater blood pressure

reduction than the comparator. I mean, you could do that. You could ask them to do that.

DR. TEMPLE: Well, they actually did do that in some sense. What's missing I think is what would happen if they added guanfacine or something like that. That you don't see.

DR. BORER: Well, that's true. We don't know what range of drugs they gave, but we didn't see how much of each component they gave. So, we really don't know whether the maximum appropriate dose or the maximum labeled dose of all the components was given. We don't know that.

That's a tough row to hoe, and I'd like to see those data. I think it would be useful for the company to go back and tease them out because that would allow us to begin to answer one of the key questions that Tom raised. But if you asked me, do I believe we would find it? Yes, I do believe we would find it. And if we did, and if the blood pressure dropped 3 over 2 or greater, then I would say the risk-benefit relationship would favor the use of the drug for the reasons that I stated about risk. It's just that I'm having a hard time identifying the population.

DR. TEMPLE: I won't ask it now but I might later. Obviously, there's not complete agreement on that 3 over 2 because I don't think Steve would say the same

thing, but that's what makes horse racing.

One possibility I guess if you did believe that a bona fide advantage of that amount was meaningful is that there could be another study in people who are refractory in some well-defined way in which people were randomized to two different approaches, including adding another drug, and you got to see if there was a persistent difference. So, maybe it's available in those data, but if it were not, I take it, that's another possibility.

DR. BORER: That would be an alternative solution to the problem.

DR. NISSEN: You kind of took the words right out of my mouth. I was going to suggest that -- I mean, this would be a very useful piece of information for us -- to take patients and to do everything you can to get them to goal using conventional agents, used aggressively with multiple opportunities for titration, and then randomize either to have them switched to omapatrilat or to continue on the ACE inhibitor that would be part of their regimen and see whether or not, in fact, you could do better.

DR. TEMPLE: But that only works if you believe that lowering blood pressure more with this drug is good. I just want to remind you.

DR. NISSEN: I understand. I'm not disagreeing with you, Bob, that lowering blood pressure is a very good

thing. I'm not disagreeing at all. But I'm trying to say that in the context of a drug with very significant risks associated with it, we just can't accept that as being sufficient.

DR. FLEMING: If I could add to the comments you were just making. You had noted, as I had stated, that I believe there is a favorable benefit-to-risk in terms of cardiovascular events prevented against life-threatening cases of angioedema, which I do believe. I don't believe that the data are as strong as the sponsor said a couple of times when they said there's an order of magnitude difference in frequencies of those events. I would have put it more as a twofold larger number of cardiovascular events, and if you truly believe in the blood pressure lowering surrogate, maybe it's two- to five-fold. But then we have the uncertainties we've been discussing about the full validity of the surrogate in this setting and about the durability of maintaining that 3 millimeter difference.

All of this would be adequate from my perspective; i.e., I would consider those uncertainties of not sufficient magnitude to cause concern to me if it weren't for the life-threatening angioedema. And it's in the context of that life-threatening angioedema then that what I worry about is even though I do see a favorable benefit-to-risk here, it seems entirely plausible that you

could readily alternatively achieve the benefit without the risk.

It's speculation -- but for what we've been talking about, and I think this is the essence of question 4.2 -- whether or not it was a design feature, so to speak, that led to these observed differences. I have serious concerns that we might have been able to have provided alternative management that would have had much lower differences in blood pressure without the corresponding risk of life-threatening angioedema.

DR. BORER: Okay. I think we've given you a great deal of opinion.

Depending upon the committee's answer in question 4, identify a target population and estimate the magnitude of expected benefit. I think we've discussed that. You don't really want us to define precisely what it means to be refractory, and we've all said refractory is what we're talking about.

DR. THROCKMORTON: Well, you've all at various times sort of said that you believed that -- and obviously, the sponsor has made proposals about target populations where the benefits were greater. I guess one useful thing would be to comment on how you would go about doing that. The sponsor has made one set of proposals, and you may find that credible. You may have alternative ways that you

might use to identify a population that might most benefit from this drug.

DR. BORER: We'll split this into two parts then and get some opinions about the target population and then make separately a comment about how one would estimate the magnitude of the expected benefit.

Why don't we start out with the target population issue. Tom, do you have an opinion about that?

DR. PICKERING: Well, obviously, I don't think anybody is suggesting that it should be indicated as first line treatment for the general population. So, there has to be some selection of people who are at increased risk. I guess my problem with this is, again, OCTAVE was designed I guess on the assumption that this was going to be something that was approvable as a first line drug, and it wasn't intended specifically to focus on any high-risk target population. So, any information that's provided is a sort of retrospective analysis. Some of the other studies that were done comparing it with other agents in the high-risk population such as the one with people with very high diastolic pressures gave data that were less convincing than some of the other data that we've heard.

So, the other area where I have a real problem is the issue of the increased risk in blacks who obviously are going to be in this country a very big portion of any

high-risk population. And I'm concerned that the angioedema rate in these patients is I think 1 in 19, and I don't know how one can separate out, to say that you shouldn't give this patient this medication to blacks. I think that opens up a whole nest egg of problems both political and how do you define who's black and who's not and also other things like that. So, I have a problem trying to define a specific high-risk population at this time.

DR. BORER: Steve.

DR. NISSEN: I don't think I can identify a target population based upon what we now know. Part of the reason I say that is that if we tried to do so by doing some kind of a subset or subgroup analysis from OCTAVE, then what we're talking about is we're trying to make a decision based upon lumping together some non-prespecified subgroups and saying, all right, well, if you had all this and this and this, it looks like you would benefit. I think that the level of evidence that you should look for here is a target population should be prospectively defined not retrospectively defined. So, I just don't like the idea of trying to carve up the data we have and use that carved-up data to try to define a population that would benefit. I don't think that's a proper in a drug with this kind of risk level, and therefore I cannot identify a

target population.

DR. BORER: Susanna.

DR. CUNNINGHAM: All I can define is who probably shouldn't have it by the risks of the angioedema, but I don't think I can really define who should have it.

DR. BORER: Blase.

DR. CARABELLO: Yes, I agree. It seems silly to give this to blacks and smokers unless there's a compelling reason to do so. And the sponsor has already suggested that it be targeted at a population in whom other therapies have failed to control their hypertension. I think that's a start, but it has to be defined more carefully than that.

DR. BORER: Paul.

DR. ARMSTRONG: I think Steve and Blase have articulated my opinion.

DR. BORER: Mike.

DR. ARTMAN: Well, I think one population would be the population that Dr. Black showed us, his patients in his clinic that are on multiple drugs in a well-controlled setting that can't be controlled. I think that would be a place to start with this, and I think that would be a very sort of quick and easy study to do. So, I think that you could try to get your hands around that defining patients who are on adequate doses of at least three drugs and still

are not controlled, that sort of thing.

DR. BORER: Tom.

DR. TEMPLE: Jeffrey, just on that last point, that's a different proposal from what the company said.

DR. BORER: I understand.

DR. TEMPLE: It says the blood pressure is what defines the population, not all these other things.

DR. BORER: I was going to comment on that just now myself.

I just made a suggestion a few minutes ago that maybe the data could be teased out of the 25,000-patient study, which is a pretty big study. But I must agree with my colleagues here who say that that may not be the proper way to go. Maybe another trial is necessary although I hate to say that, given the resources that would have to be lavished on such a trial.

But I don't think there's anything unreasonable about the target population that the sponsor has proposed, assuming that refractoriness of blood pressure is defined. They said difficult to control. I'm saying refractory which is qualitatively maybe a little bit worse. I too would say look at Henry's population that he can't control and see which one of them have the other problems and study them and show that omapatrilat adds something that wasn't added by the comparator.

I guess it would be very difficult to be reasonably certain that the benefit that I'm willing to impute to the drug, if it lowers blood pressure by 3 over 2, can be imputed unless we actually see it in the appropriate population. I think the best way to do that is to study it prospectively. It may be that the sponsor can come back with a subanalysis by searching its data that would be compelling. I don't want to rule out the possibility that that could happen, but I think the better way would be to do a trial.

DR. THROCKMORTON: Jeffrey, standard advice, when talking about sponsors about resistant populations, has been three classes of drugs, maximum doses, one ACE inhibitor, one CCB, and one diuretic, that sort of thing. Is that the sort of general thing that people -- I mean, does that define Dr. Black's clinic in some reasonable sense?

DR. BORER: That kind of construct would be reasonable to me. That specific algorithm might not be, three drugs, three different classes. But I would ask Tom for his opinion about that.

DR. PICKERING: I think that's a reasonable and commonly used criterion for resistant hypertension.

DR. THROCKMORTON: Just to go back one more time. What Bob said was important. That's a different way

of thinking about a high risk or a population that might benefit from drug, the one that the sponsor has been putting forth which was looking at cardiovascular risks and then possible benefit.

DR. BORER: No, that's not different. If I understood their proposal --

DR. THROCKMORTON: No. There were two separate sort of things.

DR. BORER: I thought it was not exclusive but inclusive. You had to have the high blood pressure and you had to have the problem.

DR. TEMPLE: Yes, but that's the question. Do you have the problems or is a systolic pressure of 160 uncontrolled by three classes of drugs bad enough?

DR. BORER: Sufficient.

DR. TEMPLE: That's what I'm asking.

DR. BORER: Why don't we start with Tom and let's go around.

DR. PICKERING: Well, I guess it's a question of what risk you want to start with. Obviously if there's the additional risk factors as well, which I suspect there will be in most of these patients, the risk will be higher.

DR. BORER: Must we demand that those additional risk factors be present to give the opinion that the drug is effective and has safety acceptable for the

intended use if all they have is refractory hypertension rather than refractory hypertension plus these clinical evidence of these other problems.

DR. TEMPLE: For those people who meet SHEP entry criteria, we know what blood pressure lowering does in those people, and they weren't selected because they had other risks particularly.

DR. PICKERING: I guess I would say other risk factors present as well.

DR. BORER: Steve.

DR. NISSEN: I actually agree with you, Bob. I think that you could define a population here. We know that people with refractory hypertension do very, very badly, and I think you could lower the bar here a little bit and I would still be very comfortable if you said show us that in a group of people we just can't control with the best drugs we've got, three of them, are still above some threshold and make that threshold significant, not above 130 over 80. I'm not sure where to set that. Because we know that people that can't be controlled despite everything we can throw at them do badly, and a drug that could get those people to goal would have enough likely advantages that it might well, in my view, if it were a robust study, outweigh the disadvantages of angioedema. I think you could define such a trial, but it would have to

be very rigorously done.

DR. BORER: Susanna.

DR. CUNNINGHAM: So, let me clarify. We're not answering number 5 here. We're defining what a future study might look like.

DR. BORER: What's the population that we want to define as appropriate for getting this drug if it works in that population? Is it just a refractory hypertension population, or do these refractory patients also have to have cardiovascular problems or other end organ problems as was proposed by the sponsor? Do we want to be that rigorous or just blood pressure problems?

DR. CUNNINGHAM: I think just refractory hypertension would be enough.

DR. BORER: Blase.

DR. CARABELLO: I don't know how to answer the question. I'm not too concerned about the other risk factors.

I am concerned about how much demand we put on previous control of blood pressure. If we say that the population to be tested in one in which we've minutely titrated every last drug before we add this one and that's the only way in which we'll accept efficacy, I don't think that's a very good standard because we've got a whole bunch of folks out there who have had reasonable medical therapy

and still are hypertensive. Now, could you get them a little lower if you beat the hell out of them and their providers? Maybe? But is that actually going to translate to benefit to the patient? I don't know. I think that this has to be taken in the context of current good but not impossible-to-reach standards.

DR. BORER: Just to ask for a further statement on that, the way it's been set forward -- and Tom indicates that this is routine practice in this area -- what we've now suggested is that to be declared refractory you should be on three classes of drugs, not necessarily five or six, but three, and that the drugs should have been titrated up to their maximally tolerable or maximally labeled doses. Would that be too much of a standard?

DR. CARABELLO: Well, unless of course going to three drugs generates so many additional side effects that now the patient won't take them.

DR. BORER: Then it's not tolerated, and I would think such patients could be included in such a trial.

Steve.

DR. NISSEN: I was just going to say, Blase, there are an awful lot of people out there that are on ACE inhibitor, diuretic, and amlodipine. There's a world of people like that and some of them aren't controlled on

that. Some are still greater than 150 over 100 on 10 milligrams of amlodipine and 40 a day of enalapril and 50 of hydrochlorothiazide, let's say. I think if you could get those people down significantly with a drug, it might mitigate the risk involved in a drug like omapatrilat. So, I think such a trial would go a significant way toward making that an approvable drug.

DR. BORER: Paul.

DR. ARMSTRONG: The patient that Steve just described is often controlled with the addition of a beta blocker. So, the notion that three should be the standard for refractory hypertension, and the addition of a new class of drug is not necessarily for me adequate, but if the patient was truly refractory to best medical therapy in a supervised hypertension clinic environment and had evidence of target organ damage, I could see taking the additional and unknown risk of adding a drug such as this, especially if that patient was being supervised by experts who understood the side effect implications and were following the patient carefully.

DR. BORER: Mike.

DR. ARTMAN: Well, I sort of made the proposal and you guys refined it a little bit. So I stand as suggested.

DR. BORER: Tom.

DR. FLEMING: If the question is in what population is it most plausible that this agent could be established to have a role, I would accept the logic of the sponsor saying that you would want to target a population that simultaneously satisfied two criteria. First, it would be patients at high risk for major cardiovascular events, i.e., so the setting where the benefit is substantial; and where it's difficult to control hypertension, i.e., where it's less likely that alternative available therapies could yield that benefit. So, in the context of having a risk of life-threatening angioedema, I want to identify a population where there is substantial up-side benefit and simultaneously a population in which I can more readily achieve that up-side benefit with this agent, even though it carries the side effect.

DR. TEMPLE: Jeffrey, there really have been two slightly differing themes, and it's important. We know from SHEP that being 70 and having a systolic of 160 is a high-risk situation by definition. How much more than knowing the blood pressure do you all think that the entry population in this other study would have to have?

DR. BORER: You've heard a couple of opinions already. I think there's a slight preponderance in favor of blood pressure alone being sufficient. And I'm going to add my voice to that. While I'd love to see people with

all the end organ problems in the population, I'm sure they will be, as Tom pointed out, just by the nature of the beast, but I would accept uncontrollable blood pressure alone as the population to study, uncontrollable by the definition that we've used.

DR. NISSEN: Jeff, if I could just add. It would be nice also to have that trial not be a 24-week trial because I think one of the things that really limited the current design was there really wasn't enough time to see potential differences emerge here. If we're going to do it, it ought to be pretty solid.

DR. TEMPLE: That's a very important question. If you're not looking for end organ damage and you're really just now looking at the substitution of one drug for something else in the regimen, you don't need a very long trial to do that. Why would it have to be more than 8 weeks?

DR. NISSEN: Well, because I would not want to preclude the addition of other drugs to either regimen. In other words, some people like the idea of adding a beta blocker, and I'd like both arms to have that open to them.

DR. TEMPLE: No. That should be done before they even get into it.

DR. NISSEN: That means four drugs, though.

DR. TEMPLE: Whether it's three or four is no

matter. They're refractory and then you randomize to substituting this and keeping the same regimen.

DR. NISSEN: That would be certainly one way to approach it. I don't think we can design the trial at this table, but I think what you're getting from us I think is the sense that showing efficacy in a truly refractory population, well studied would be meaningful.

DR. TEMPLE: No. I've got that. It was the 26 weeks that threw me.

DR. NISSEN: Well, I guess part of it is that I'm always more comfortable when the exposure is a little longer and when you have a little more observational time. Part of it relates to the fact that I think there are some major risks associated with this drug. I guess I don't think we've characterized them very well.

DR. TEMPLE: Yes, but the study we're talking about is going to be small compared to OCTAVE, as is any study in the world. So, it's not going to get you much more safety information, at least as I'm hearing it. It's going to document unequivocally that you control people that were uncontrolled before. That's a very limited thing. It's not very hard to do if it's true and it shouldn't take 26 weeks if that's enough. But you need to be clear.

DR. NISSEN: Let me see if I can be more

specific. Again, I hadn't really thought of this before I came in here. But also we'd like to know that the differences are stable, that they're not differences that are closing with time. Tom Pickering raised this question earlier. So, I personally would be a lot more comfortable if I knew that you could sustain for a year an advantage in blood pressure because it's going to be a smaller population, so it's easier to follow them for a little bit longer and see if you can get that kind of sustained benefit in this population. If they escape after 24 weeks, then you don't gain very much.

DR. BORER: I'd like to comment on that also. I'd love to see a very long trial. On the other hand, that's not a standard that we've ever set for an antihypertensive drug because there hasn't been any compelling evidence that problems develop late because we didn't run the trials long enough.

I would be perfectly happy with a 6-month trial, which is longer than the usual antihypertensive trial. I'm concerned, as Steve says, about exposure for safety, but if it's a small trial, we're not going to get much from that. I'd like to know, though, from the sponsor of the 25,000 patients involved in the trial, 12,000 were on omapatrilat. Have they been continued in an open-label experience or any subset of them?

DR. LEVY: No, they haven't.

DR. BORER: You did show us, though, some 1-year data in a withdrawal study that showed persistence of effect at 1 year, which I find sort of compelling.

DR. TEMPLE: I was going to ask you that. There's a lot of data that goes long. There isn't any suggestion that whatever effect there is goes away. It's really important. For one thing, I would be damned uncomfortable allowing a trial to continue that showed a difference and not doing something else to get those people under control. I think that would be dubious. We allow 8-week trials against placebo, but we don't allow 26-week trials against placebo.

DR. NISSEN: But, Bob, you've already said these are people that can't be controlled any other way.

DR. TEMPLE: No. There's a fifth and sixth and seventh and eighth drug too. Somebody would have to go do something.

But my fundamental question is, what's the question? I thought, from all the previous discussion, the question was can you take people who are bona fide refractory and who are refractory at entry -- they're on all these drugs at entry -- and get control when you couldn't before, a question that I would have thought could be answered in 6 to 12 weeks tops.

DR. ARTMAN: I think that's right. I think that is the question and I think it could be done in a relatively short trial because I think under that circumstance, we would be happy to see that incremental reduction in blood pressure if it were true in that population.

DR. FLEMING: In the absence of angioedema, I could be persuaded to accept that, but part of the fundamental issue at hand here is to be convinced that we're going to get a difference, sustained for adequate duration, that it will offset a very real and important side effect. So, coming back to what you were saying, Jeff, this isn't the standard situation. If there wasn't angioedema, one would be more permissive here and would be less concerned.

DR. THROCKMORTON: Absent angioedema, we wouldn't be here.

DR. TEMPLE: But you already have data on whether the effect of this drug is evanescent. So, why do you need to answer that question again?

DR. NISSEN: We have that data relative to placebo I think. We have it relative to an active control arm with three drugs. Do we know that?

DR. TEMPLE: Well, you could say OCTAVE answers that question to a degree, couldn't you? They didn't add

on other drugs or push the dose, but you do have that difference persisting.

DR. BORER: I may have missed something, but I thought the withdrawal study you did was in a trial against enalapril, was it not?

DR. LEVY: No. Let me just clarify. I did show you data from a 1-year-long losartan controlled trial in which the blood pressure differential was maintained. I commented on the results of a withdrawal study. That was conducted in patients being followed in a long-term open-label extension, and they were randomized to continue treatment with omapatrilat or to withdrawal to placebo, and a difference in blood pressure emerged very quickly.

DR. BORER: That's fine. Thank you for the information.

To me those are pretty important pieces of information if you were able to maintain for a year a differential against an active comparator and you were able to show a difference on withdrawal to placebo after a year, I'm not sure that we have any information from any body of data that would suggest that people who are really severely ill would be less likely to maintain the effects of a drug. They may be less likely to remain in control, but then again that's what blood pressure cuffs are for, to find that out, and then you can alter the regimen.

But, Tom, is there any reason to expect that a severely hypertensive population put on a drug and responding to the drug will lose their responsiveness to that drug after a year as compared with somebody with mild to moderate hypertension?

DR. PICKERING: I don't think so necessarily, no.

DR. BORER: I would say, although I absolutely agree we'd like long-term experience so that we can get a better sense of safety and all those things, I don't think it's necessary to mandate a long-term trial to show the persistence of effect. I think they've already done that.

But you want to get the opinions of everybody around the table. You've just heard Tom's. Susanna.

DR. CUNNINGHAM: I think I'd take 6 months' worth.

DR. BORER: Steve, you already gave your opinion. Mike, Tom. Okay.

I think we've sort of dealt with 6, but I think we need to do it formally. Should omapatrilat be approved for the treatment of hypertension? Let's deal with that first, and then depending upon the answer, we may go to 6.1, 6.2, and 6.3. Steve.

DR. NISSEN: My answer is no, and I think the reasons have come out in the discussion. Mainly they

relate to the fact that we have limited data on the effect of the drug on events which would have strengthened the argument and that the risk of angioedema is substantial enough to mitigate against the potential benefit of the lower blood pressure.

I would like to say that I see two potential routes to approvability from my perspective. One we've already discussed, which is a trial showing that people that are absolutely refractory can be controlled or have a better blood pressure result when omapatrilat is substituted for an ACE inhibitor adequately done.

But the other which I think should not be ruled out is to show that in fact in a broader population, there is a morbidity and mortality advantage that outweighs the angioedema. Tom and others and the company have tried to estimate the ratio of benefit to risk, but measuring it would be the most compelling evidence of all. So, if one could define a population -- if I were going to do such a study, I'd probably pick people at pretty high risk, and I'd try to show that there was a morbidity and mortality advantage in that population that really quite significantly outweighed the very real risk of angioedema.

The advantage of such a development program is that it would allow this drug to be used in a broader population, not just in the absolutely refractory patients,

but in other patients because it may be that the company is right. There may be an order of magnitude benefit greater than risk in a relatively broad population. And if that were proven, then I think it would be a slam dunk that we'd accept the angioedema and we'd counsel about how to do everything possible to prevent it and all that risk management stuff, but we would be pretty comfortable that that overall would help the health of this population.

DR. TEMPLE: Just to be sure, would this be a trial in which people were allowed to be better controlled on omapatrilat than on the other drug, or would this be a case where they would have to show that using that is better than the other thing even though there's equal control?

DR. NISSEN: You know, I'd have to think about this. Again, I'm not sure I can design the trial at the table here, but I guess I would like to see in such a trial a design -- because it would be a longer-term trial -- then the opportunity for titration of the active control arm would continue as would the opportunity for titration of the omapatrilat arm. So, you'd really be looking for whether or not a regimen containing omapatrilat, when optimally delivered over a long period of time, would have a better efficacy at preventing morbidity and mortality than a conventional regimen titrated to optimal effect over

time.

DR. TEMPLE: But their hope is that the way it would do that is by giving better control, and if you obliterated better control, then it would have to be through some magic thing.

(Laughter.)

DR. TEMPLE: They don't have a proposal like that.

DR. NISSEN: And if it obliterated better control, then there's no reason to ever use omapatrilat. So, I guess the point would be if you can't produce a persistent differential in blood pressure, then there's no reason for us to use this drug in a population we can achieve that control with conventional agents in.

So, I think you have to let both arms be titrated and you'd probably want to do it more rigorously than was done in OCTAVE, meaning mandate up-titrations. I have to think about it a little bit, but the idea is to try to show that there is a clinical advantage to regimens containing omapatrilat with respect to some harder endpoints other than just blood pressure.

Again, I'm not putting down the surrogate. I'm with you, Bob. I think the surrogate is a good surrogate, but it's only relevant when you have a drug that has comparable risks to what else is out there. So, when you

don't have that, then I think you've got to go to those harder endpoints. I think it could work. I think you could find that over 3 years or 4 years that a regimen containing omapatrilat will end up with a blood pressure differential that's maintained and that leads to a difference in hard events, in which case this drug would be a good drug to make available for a broader population.

DR. BORER: Tom Fleming.

DR. FLEMING: I agree very much with the essence of what Steve has said, and in the interest of avoiding repeating that and other things that I've said before, I'll just state that for those reasons I vote no.

DR. BORER: Mike.

DR. ARTMAN: I would vote no at this time.

DR. BORER: Susanna.

DR. CUNNINGHAM: No.

DR. BORER: Blase.

DR. CARABELLO: I'll be the one dissenter and vote yes. I believe that if the drug were added to the community now, it would result in a substantial fall in blood pressure in our hypertensive patients. For me, it's not the question can it, under the rigorous controls of the trial, make a difference, but what difference would it make in the community in which apparently we as a medical group are doing a lousy job of controlling people's blood

pressure. And I think it's that group of people that I'm most interested in. I think that the risk of truly life-threatening angioedema could be controlled.

DR. BORER: Reluctantly I'm going to vote no, and this is a very difficult vote and sort of a close call because my intuition is that this drug would offer a benefit that we don't get with other agents. But I'd like to see the data in a refractory population, defined as we've all discussed, that it does indeed improve blood pressure control because there's a countervailing risk which I think can be superseded by the benefit of the additional blood pressure lowering, but I'd like to see that. So, I don't think this is not an approvable drug, but I don't think it's an approvable drug today.

We don't have to go to 6.1, 6.2, and 6.3.

Bob.

DR. TEMPLE: I just want to thank the committee for struggling with what was a very difficult set of issues.

DR. BORER: Doug.

DR. THROCKMORTON: Yes, I'd just echo that. The materials and the issues you've been asked to look at over the last couple of days have been very challenging, and the agency really thanks you for your help. It's truly valued.

DR. BORER: And it's only 3:53 and 52 seconds.

(Whereupon, at 3:53 p.m., the committee was adjourned.)