language I think.

DR. TEMPLE: It's what I said. It says something about the drug itself. There have not been comparative claims of that kind. You could argue about whether that's useful, given that the whole class is known to behave in a certain way, but I sort of hear positive thoughts about such things because they might be useful. I just want to be sure I'm interpreting you correctly.

DR. BORER: If I understood correctly -- and I'll let her speak for herself -- what Beverly was suggesting was that it would be very legitimate if someone wanted to come forward and do those studies and do them and show that a certain drug is better in a subpopulation, in a minority population, whatever, than another drug, that that would be a reasonable thing to do, but not that every package needs to show that.

Steve, you had another comment?

DR. NISSEN: Yes. Here's the question I would ask; at least I asked. What do clinicians need to know in order to optimally care for patients? Somebody walks in my office with isolated systolic hypertension. If there is a drug out there that works better in that population than another drug, would it be useful for me as a clinician to know that? If it could be proven satisfactorily to everybody involved, the answer is you bet. Or in African

Americans. So, when it's clinically relevant, when there is a population out there, we have to decide which drug to use. Right now we don't have much information about that and I think that would be potentially very valuable to clinicians.

Similarly, many patients that we see particularly with diabetes are on poly-drug regimens, complex regimens where it's tough to control the blood pressure. If some combination or permutations of agents had a particularly synergistic effect such that we could get better blood pressure control by combining agent X with agent A rather than agent Y and if that were really robustly shown, then that could have a really big impact on how we think about this.

For example, if adding a drug to a diuretic, if drug A added to a diuretic does a better job than adding drug B, even though compared to each other, they may not be very different, then that's useful information for clinicians, and if it can be proven satisfactorily, I'd like to know that and I'd like that to be in the labeling.

DR. BORER: Paul.

DR. ARMSTRONG: I guess it would be helpful, Bob, -- and maybe in the workshop you're going to organize, you can deal with this -- the extent to which the label should become an advocacy statement for education of

physicians and doctors and used by the drug detailers to impact favorably on the care of patients.

DR. BORER: Tom.

DR. PICKERING: Yes, just a word of concern about saying that a drug works better in one ethnic group than another. When ACE inhibitors first came out, the word was that they didn't work as well in blacks as in whites. I think there was genuine concern that African Americans were not getting some of the benefits of ACE inhibitors they might have otherwise have been getting, independent of the blood pressure effect. In fact, you can get the same effect with just increasing the dose and combining it with a diuretic.

DR. BORER: Have you gotten all the advice you need about this one, Doug?

I'm sorry. Tom.

DR. FLEMING: I'd like to go back then to Paul's answers to questions 3.1 and 3.2. Paul, I think you had said yes to 1 and no to 2.

We had talked a bit, when we answered question 2, about a scenario where the comparator might have substantial evidence indicating that a bi.d. regimen would be more effective in its delivery than a q.d. One might imagine that the once-daily antihypertensive experimental regimen, let's say, yields a 6 millimeter drop, and if you

compare it to the comparator's once-daily, you would see superiority at 6.4. But it's already known that the comparator is much more effective at b.i.d. And let's say it would be 10. So, it would be inferior. It would be 6 against 10.

In general, my answer, I thought, would have been you want to compare to the comparator's most effective approved regimen if there's evidence strongly indicating that the comparator is more effective at a different schedule. In the setting in which there isn't such evidence, and the evidence suggests that q.d. and a different schedule would be relatively comparable in efficacy, then I can understand that it would be, as you've indicated in 3.1, appropriate to compare it to the highest approved once-daily dose.

But in those settings where there's considerable evidence that the comparator is more effective in a regimen other than once-daily dosing, then to claim superiority, I would think we would have to be superior to that optimal delivery of the comparator regimen.

DR. BORER: For the record, Paul already agreed with you when Doug clarified his question, that 3.2 would be a reasonable basis for a superiority claim.

DR. TEMPLE: Tom is saying it's necessary. I believe several people said not necessarily if the drug

that doesn't work as well once a day has a once-a-day claim. So, a lot turned on what the nature of the claim is.

DR. BORER: Do you want a more complete clarification of the answer to that?

DR. TEMPLE: Well, we should be sure that we've heard you correctly.

DR. FLEMING: Let me just emphasize this. What I'm suggesting is if there is an approval for the comparator agent at q.d. and, for example b.i.d., and there's considerable evidence that b.i.d. for that agent delivers greater efficacy, then if I want a superiority claim against the comparator, I'm suggesting that it would be necessary to have evidence of superiority against its known more effective schedule.

DR. BORER: Beverly.

DR. LORELL: I agree with that.

DR. BORER: Mike.

DR. ARTMAN: Yes, I agree with Tom.

DR. BORER: JoAnn.

DR. LINDENFELD: I'm not sure I agree with that. Let me just be sure I'm clear. But I think if the less effective drug is approved for once a day, then I as a doctor in the office want to know if I can give another once-a-day drug and it's better just once a day. So, I

think even if the drug is more effective at b.i.d., if it's approved to be given once a day, then I think it's fair to say that these two drugs compare and one is better once a day, and then you can make it clear that the once-a-day drug, the more effective one, is not as effective as against b.i.d. But giving once-a-day drugs is important, if I understand your point.

DR. FLEMING: Well, this might be a situation that doesn't exist. I.e., if the comparator agent is known to be more effective at, let's say, b.i.d. than q.d., would there be a setting where it would be approved in both schedules?

DR. TEMPLE: It could be if it lowers the blood pressure at trough by 4 millimeters of mercury or so, which is not so different, we might approve it even though the peak effect was bigger. There are some cases where that's been true, and we'd try to give as much data as we could so that people could make a judgment about how they were doing. But obviously some people, if they were controlled to the physician's satisfaction with the once-a-day regimen might choose that because they would conclude their patient is more likely to take it. So, there could be cases like that. Not with this class which seems to have an effect that outlasts its blood levels to a degree, but with calcium channel blockers, you could have that certainly

where the effect is relatively evanescent.

DR. THROCKMORTON: But we do first start out saying, yes, it has potential to be a once-a-day drug or not. Certainly if that's not demonstrated, you're right. We'll say if you gave tons of it to sort of symptom levels at peak, you might eke out a trough. That isn't something that we're interested in.

The typical label for this class tends to describe the use at once a day up to maximum dose and then when available what to do after you reach that top dose. That may mean that you double up the dose, you drop back and go to b.i.d., what it is, add a diuretic, what the available data suggested. And that's sort of the flavor of these labels.

So, what I'm hearing is if that's the flavor of the label, if the label has a sort of once-a-day feel to it, then that's an adequate comparator. If the label has a twice-a-day dosing, it doesn't even raise the issues of a once-a-day possibility, then obviously, as you said before, that wouldn't be a fair comparison.

DR. TEMPLE: There are also some in between. I may misremember this, but for at least one beta-blocker -- but since I'm not sure, I won't name it -- it said usually you should use divided doses, but some people may be controlled by a once-a-day dose. That's sort of in

between. That suggests that usually you need multiple doses, but somebody might get away with --

DR. FLEMING: And in that setting in particular, I would think it would be compelling to argue that you would need to be comparing to the b.i.d. dose.

DR. BORER: Okay, the unusual setting notwithstanding, my opinion would be identical with JoAnn's. If the drug is approved for once-a-day dosing and people can expect that it would be effective for once-a-day dosing, I think it's very reasonable to claim superiority for once-a-day dosing, but you have to be very careful about the way the label is written so that there's no implication that something else is also true that hasn't been studied.

Paul.

DR. ARMSTRONG: Just to clarify and come back to Tom's point, my view would be if we're talking about changing a label for comparison of drug X to compare with drug Y, that first we look at the comparison at once a day, and secondly we say drug Y, which is already approved for twice-daily dosing, because it's germane to the discussion we're going to have later, you cannot claim superiority to an efficacy dosing regimen that's been approved only on the basis of once a day. So, the caveat has to be that there may be a more effective way of administering the drug that

you're trying to claim superiority over. There I think the principles of fairness apply in the label and are clear.

DR. BORER: Steve.

DR. NISSEN: Bob, there are some shades of gray here I think. Let me see if I can help to clarify that. I can imagine a drug which is somewhat more effective b.i.d. than q.d., where as a clinician, in a patient that's near to their target blood pressure, I might give the drug once a day because of the convenience effect. But to get maximum efficacy in a patient that's much harder to control, I'd go to b.i.d. So, that shade of gray here means that we've got to be careful. So, beating up on a drug simply because it has q.d. in its label somewhere that you can give it q.d. I don't think is right.

So, I agree with Tom and I don't agree with Jeff or JoAnn. I think that it depends, and it depends a little bit on what the peak-to-trough ratios really look like. I might use a drug with a .5 peak-to-trough ratio in certain patients, and that's fine, but then I might well recognize that giving that drug b.i.d. can get a pretty much bigger effect, and therefore I wouldn't want somebody to be able to say that their drug is superior to such a drug when, in fact, we know that that drug can work pretty well b.i.d.

DR. TEMPLE: Well, they're not saying it's

superior. They're proposing to say that when you use it once a day, it gives you a difference of X millimeters of mercury. The proposal didn't say how big the difference was, but we would include what the difference was.

DR. NISSEN: No, but you know, in the nuances of what a detail person is going to do, once you give them that superiority claim, they're going to ram it down everybody's throats. I just think it's potentially a mistake here. We're very fortunate here I think that we have drugs that have very similar peak-to-trough ratios. It makes it very clean. But it may not be so clean next time, and I think we've got to be careful.

DR. TEMPLE: Let me mention one thing. You have one other thing here too. The usual reason we worry about peak-to-trough is that we're afraid the pharmacologic effect will emerge and then disappear. What that means is that if you give the drug that ought to be given twice a day in a single dose early, it ought to be showing its maximum effect if the usual thing you're worried about is here.

Well, here the differences were observable both at peak and trough. So, one of the things you might worry about is not present here. That suggests that it wouldn't make much difference even b.i.d. Of course, we don't know that.

DR. BORER: Blase.

DR. CARABELLO: If you have two drugs that are both labeled for once-a-day dosing and one is superior, I think it's perfectly legitimate to make that claim of superiority. If it turned out that in that context you had two drugs where one was superior at once-a-day dosing while the converse was true with twice-a-day dosing, you simply make the label say that, and then there's no question. I don't think these two issues need to be in conflict as long as the label states the truth.

DR. BORER: Susanna.

DR. CUNNINGHAM: I would agree that I'd like both pieces of information and have the label say it. But I also think we have to worry about what people will really do, and people are most likely to take things once a day and less likely twice a day. So, that's another piece that's going to add in in the real world.

DR. BORER: Tom.

DR. PICKERING: I would say there's no simple answer to this question and you have to judge each case on its individual merits and look at the time course of the two drugs being compared in each case.

DR. BORER: Now, do you have as much advice as you'd like?

(Laughter.)

DR. TEMPLE: Oh, yes, we got a lot.

DR. BORER: I neglected inappropriately at the beginning of the session after the break to ask if there are any speakers who want to say anything in open public hearing. We had nobody sign up to do this, and that's why I didn't ask the question. But is there anyone who needs to make a public comment?

(No response.)

DR. BORER: If not, we'll go on to question number 4. Paul, why don't you just read it and go through it.

DR. ARMSTRONG: Is it possible to claim superiority if the comparator has other outcome benefits not demonstrated by the test drug? I would say yes, most certainly.

On clinical endpoints in hypertensive patients, for example, stroke reduction? Yes, enthusiastically.

And in other populations such as those with heart failure, diabetic nephropathy, for example? And again, I would say yes.

And then the final question in that section of question 4 is, is it possible to claim superiority if the comparator has fewer potential pharmacokinetic interactions such as those related to CYP 2D6 or CYP 3A4 inhibition? And I would say no unless there was clinically relevant

drug-drug interactions or special populations where these kinetic interactions were shown to have clinical significance.

DR. BORER: Can I ask for a clarification there?

DR. THROCKMORTON: Jeff, I'm sorry. We left a phrase out of here, and I think it changes, a bit, the sense of this. I'll paint the scenario.

The question I believe should read is it possible to claim superiority as an antihypertensive, that is, just measuring differences in blood pressure if the agent you're comparing yourself with has some other effect. So, an example would be you are comparing yourself against ramipril and measuring only differences in blood pressure. How would you factor in the description of the HOPE trial that's in the approved labeling for ramipril? Would that mean that showing a difference in lowering blood pressure isn't ever enough to describe in labeling, or is it something that's always useful to describe in labeling, someplace in the middle presumably?

DR. BORER: Paul, do you want to start on that one?

DR. ARMSTRONG: So, you're rephrasing all of question 4. Is that correct? Or just the last component. I'm a little confused, Douglas.

DR. THROCKMORTON: Just 4.1 refers to lowering blood pressure compared to doing other things where clinical outcomes have been measured.

DR. TEMPLE: The question really is suppose blood pressure isn't the whole story for this drug. Is it okay to concentrate on the blood pressure effect when there's outcome data? You could ask the same thing about cholesterol-lowering drugs. The fact is that some of them have comparative data on cholesterol lowering when there are existing considerable differences in how much outcome data they have. But what do you think about that?

DR. ARMSTRONG: Well, I strongly advocated, in one of the earlier questions, for intermediate surrogates between blood pressure and stroke. So, I think my stance on this particular one is pretty clear. I don't know whether it's good enough to add a new drug to the ones we have in our armamentarium that lowers blood pressure and doesn't do the other things that some of the drugs that lower blood pressure do that are good for patients. Is that helpful?

DR. BORER: Can I just, again, try to get a clarification here? It seems to me that when we recommend that drugs should be approved for their capacity to lower blood pressure, we're immediately making the inference to ourselves in that approval that we're approving a drug

that's going to reduce the rate of myocardial infarction, stroke, cardiovascular death, renal failure. That's a given. That's what a surrogate is.

There are two possible interpretations of the question. One is do we have to show that the drug is also better than some existing approved drug for outcomes, and if that's the case, I would say no, it shouldn't be necessary to do that. But the other possible question is, if we believe the new drug is better and we show it somehow -- and let's not talk about how we show it because that's a very different trial design possibly, but if we could show that a drug were better, would that be a basis for a superiority claim? Am I somewhere in the range of what you're asking about?

DR. TEMPLE: Let's take an example. You, last visit, urged us to approve two drugs, including the comparator agent here for use in type II diabetes to prevent the progression of renal disease. Okay. So, when and if we get around to doing that and agree to it, losartan will contain a claim that it's useful for that. Okay.

The question here is, does that make you want to think in any way differently about giving a claim that once-a-day therapy with candesartan lowers blood pressure better than losartan? Should we factor that in in some

way? Should we say something about it? Should we not allow it?

DR. BORER: That's a complicated question.

DR. TEMPLE: That's why we pay you the big bucks.

(Laughter.)

DR. BORER: Some relatively quickly stated opinions around the table here about that. Steve.

DR. NISSEN: Yes. I would say one should be very, very careful here because what it would mean is let's suppose somebody came along with another ACE inhibitor and showed that it was superior at blood pressure reduction to ramipril. If we said that HOPE trumps everything else, then you could never give a blood pressure claim to another drug because HOPE has got that 10,000-patient, albeit horribly flawed in my opinion, study that showed a purported clinical benefit. But you're giving them that claim, and so if that trumps everything else, then you've got a really big problem because then any drug that wants to come along in the class and say we've got a better blood pressure effect would have to do a HOPE-sized endpoint trial in order to get a superiority claim.

I think what one could say in such labeling is that drug X had a greater blood pressure lowering effect than ramipril, although it has not been proven to have a

superior effect on X outcome. And then I think you've covered yourself. So, you may want to put it in the label, but I think to say that you can never give a claim for a surrogate once you've given a claim for a hard endpoint I think is going too far.

DR. BORER: Why don't we start at that side of the table and just go around and get a quicky opinion here. Tom.

DR. PICKERING: Yes, I guess in this context we have the LIFE study, and I would agree with Steve, that any claim has to be very specifically focused on blood pressure reduction and there may be subtle nuances where you say it's a better antihypertensive. That doesn't distinguish between whether it's better at blood pressure reduction or better at preventing complications. So, I think it has to be very specific to blood pressure.

DR. BORER: Susanna, any additional thoughts?

DR. CUNNINGHAM: I think I'd always like to know it prevented events. If I was going to be taking something, really my concern is that the event I'm going to have, not my blood pressure per se. So, I think we've got to be very careful. This is very difficult to give a yes/no answer to. It's going to be a maybe answer, and it needs to be as specific as possible.

DR. BORER: Blase.

DR. CARABELLO: If you had a drug that was superior in lowering blood pressure but clearly was inferior at other endpoints, I think it would be very difficult to allow the claim of superiority to stand. Let's say we were comparing hydralazine to propranolol when they first came out. Well, at their maximum dose, I guarantee you that hydralazine lowers blood pressure more. Would we have wanted to go on record as saying hydralazine is a better drug than propranolol? I think not.

DR. BORER: Paul, do you have any additional?

DR. ARMSTRONG: I think this is slippery and I think it's time to change in relationship to blood pressure lowering.

DR. BORER: I think that what Tom said and what Steve said are most appropriate; that is, if a drug is being judged as an antihypertensive drug and blood pressure is what's been measured and other things haven't been measured, that it's fair to give a superiority claim for blood pressure lowering, if the data support that, and perhaps it's appropriate to say, but we haven't studied the other things or something like that. We're not going to wordsmith here.

I think the issue that Blase raises, which is a very important one, about a drug clearly being inferior on events would be an important consideration if we had the

data to show that. But we don't. In fact, I don't think we ever have. So, there would be an important consideration.

But should a drug company, sponsor, be held to the standard that it is necessary to do the other study to show superiority or inferiority or equivalence on the non-blood pressure endpoint, I think that's too high a standard. I think that's a separate issue. We all accept that from Dr. Kannel's data that the more you lower blood pressure, the better off you are, to a certain extent until you faint. Therefore, if one drug is better than another for that purpose, that's something that should be known and can be legitimately factored into clinical decision making. So, I think it's a reasonable basis for a superiority claim.

Tom, do you have any other comments about that issue?

DR. FLEMING: Well, this is a situation that troubles me greatly in using surrogates. Ultimately what I want to be superior with respect to are the clinical endpoints, superiority in reducing risk of stroke and MIs and death. If I am superior in blood pressure control, then it's certainly acceptable to claim superiority in blood pressure control. And that's one mechanism by which you would be influencing the occurrence of those other

events.

But in a setting, which I think this question is posing, where I know the comparator has evidence of other effects or other mechanisms of action other than through blood pressure control whereby it's achieving clinical benefit, then I think it's misleading to simply state that the study has shown better blood pressure control. I think you have to give a more global presentation of the results. There is evidence of superiority in blood pressure control, but I think you have to then indicate where there are these other superior benefits of the comparator so that someone can make a more informed judgment about global benefit to risk.

DR. TEMPLE: You don't know about superior benefits. All you know is that they've found something that the other one hasn't. You could, in some sense, say as soon as one member of a class gets an outcome claim, all the rest of them ought to be labeled that we don't have that outcome claim. Now, that's not crazy, but it would be radical.

DR. FLEMING: So, basically there are two ways of reading this question when you say not demonstrated by the test drug. It could be that the test drug has been assessed and the benefit wasn't demonstrated or that you haven't even looked for it yet. And those are distinct

circumstances. The former circumstance is what I consider to be especially problematic.

DR. BORER: As a practical matter, what Bob says I think is very important. Ramipril received a labeling claim on the basis of the HOPE trial. No other ACE inhibitor has that claim, and in fact if you wanted to use another one for that purpose, I would suggest that we don't know what dose to use, whereas there was a dose-response curve shown in the HOPE trial. So, you have a lot of information there.

But, as Blase and I were discussing earlier, if somebody gets his or her medical care at a Veterans Affairs hospital, you can't get ramipril for the indication that we're talking about. So, people wind up perhaps using other ACE inhibitors without the data. So, the point is well taken that if we don't have these data, it's hard to penalize a drug for not having data that we don't have when there are data that may be relevant for other purposes. Well, enough said.

JoAnn, do you have any other thoughts about this issue?

DR. LINDENFELD: No. I would just agree. I think it's fair to say that the blood pressure control is superior if there are no concerning data that there might be other events that are bad, and then in the labeling to

take care of the idea that we just don't have the same outcome data as we have with the comparator.

DR. TEMPLE: Well, on the last, though, I just want to emphasize, for example, we don't have all other ACE inhibitors labeled saying I'm not ramipril or I'm not this or that.

DR. LINDENFELD: But they're not specifically compared to ramipril, are they, in the labeling?

DR. TEMPLE: No, but they lack the data that ramipril has. If they were directly compared, yes, we're not burdened by that --

DR. LINDENFELD: But here you're asking to say that one drug is specifically better than another individual drug, and so I think if you want that claim, you should say that we don't have the same outcome data with the other specific drug that we're claiming to be superior to in blood pressure. I think that's a little bit different situation.

DR. TEMPLE: Well, that is.

DR. NISSEN: A very important point that JoAnn makes. I think what she's saying -- and I agree with it wholeheartedly -- is if somebody came along and said, we lower blood pressure better than ramipril and I want a claim, then you also force them to add to the label that they don't have the outcomes data.

DR. TEMPLE: Before we leave that, the claim that the comparator agent might get, based on your recommendation, doesn't really clearly have anything to do with its blood pressure control. Remember, these drugs were compared with calcium channel blockers that lower the blood pressure just as much. It seems like it has more to do with something else. Is that still something that ought to be included in there? Keep talking.

DR. BORER: At the next meeting.

Mike.

DR. ARTMAN: I agree with what's been said. I think that it's a little easier when you have these, as Steve pointed out, within-class comparisons. When you're comparing drugs that have antihypertensive effects across classes, then that's where I think it gets pretty dicey. I think it's very difficult to give a simple yes or no answer to this. I think I would agree with what's been said about explicitly clarifying those issues in the labeling.

DR. BORER: Beverly.

DR. LORELL: I think this is a very slippery issue. I think a couple of points that were made are very clear, that if drug A demonstrated a claim of superiority over drug B on a surrogate endpoint, but that there were other endpoints that were formally tested that were negative, that must be said in the labeling.

I think the second instance is that if drug A is seeking a superiority claim for a surrogate endpoint over drug B and demonstrates it, but drug B explicitly has gone a step further and demonstrated a major endpoint that's present in its labeling, I think that in fairness to consumers and those who prescribe drugs, that must also be stated.

However, I agree with your point that I don't think it should be required in labeling to state something that has not clearly been tested, where there's uncertainty as to whether something is explicitly a poorly understood property of a drug versus a class effect.

DR. BORER: Okay. You now have a great deal of thinking recorded, and I'm sure we'll revisit this again. But for now, let's go on to number 5.

Yes, Tom.

DR. FLEMING: Well, have we covered this adequately, Bob?

DR. THROCKMORTON: We're going to give you a chance to revisit this when you come to tell us how to label any of these products. We'll be asking you the specifics around these particular products. I think that will give us some additional insight.

DR. TEMPLE: I admit to some difficulty about what I hear at least some tendency towards suggesting,

which is fine, mention that the blood pressure effect was bigger but add a series of caveats that say, but they haven't shown the outcome data yet for this. We don't regularly do that. Other sartans don't say, won't say we don't know whether we have the effect that some of them have on type II diabetes. It's not that one couldn't do that, but we tend to remain more agnostic perhaps to help your HMO know what to do because we don't know whether it's more sensible to assume that members of a class all behave the same or to be rigid about saying if you haven't shown it yet, you don't get it yet.

And we certainly have not, though, as a matter of practice, which one could say would be informative, said as soon as we gave a claim to one of them, relabel all the others saying they don't have this claim. The suggestions I think move a little in that direction. So, that's a lot to think about.

DR. THROCKMORTON: Well, the argument is that because it's a strict comparison against that drug, there's a higher burden of labeling. I think that's what I heard.

DR. ARMSTRONG: But isn't it also an issue of whether the measurement is a surrogate as opposed to a direct indicator of the disease process where we get into this? In other words, the surrogate may go the opposite way to the very thing that we want to modify and that

conversation can be segmented around that kind of class of agents.

DR. TEMPLE: But in the example we're talking about where we see a difference in a blood pressure effect, we really don't know whether that has anything to do with an effect in type II diabetes. We wouldn't let anybody say anything like that. So, I don't know if that's the relevant surrogate for the effect in type II diabetes. Maybe it is. Maybe it really was the blood pressure, but maybe it's really something vascular that is quite a different matter. So, to add but we don't know whether it has this effect -- well, it's troublesome. We'll certainly think about everything that you've said.

DR. BORER: Beverly.

DR. LORELL: Well, but I think you just made a very important comment, that when you're seeking a claim explicitly for superiority between drug A and B --

DR. TEMPLE: On blood pressure.

DR. LORELL: -- whether it be for hypertension --

DR. TEMPLE: Only on blood pressure.

DR. LORELL: For blood pressure. But the notion of superiority in a claim and in marketing and in what consumers are going to be doing carries some extra burden of labeling in my opinion. So, if drug A is

specifically compared to B for superiority, but B has shown something otherwise very important in a long-term outcome measure, then it needs to be stated in the labeling. It can be simple labeling, but I think the superiority claim carries a higher level of statement.

DR. TEMPLE: Makes it more necessary.

DR. BORER: Tom, hold just one second, if you will. In deference to the need to complete this review this morning sometime, let me ask if it's okay that we table the remainder of the discussion on this particular issue that is a more generalized issue than the question we're being asked to focus on because of this NDA, and maybe we can get to some of the specifics in the later questions or at another time.

DR. THROCKMORTON: That's fine. Actually I think, Jeff, question 5 was generally asking these studies are often hard to do. How enthusiastic is the committee at encouraging sponsors to continue to do them? I haven't heard any lack of enthusiasm. So, unless someone thinks that we should say this is useless and we shouldn't encourage it, I think we could probably move to question 6.

DR. BORER: Does anybody think we shouldn't encourage more comparative studies?

(No response.)

DR. BORER: Nobody seems to.

DR. THROCKMORTON: In antihypertensives.

DR. ARMSTRONG: I was just going to say as long as they're addressing relevant questions, it would be safety or compliance or even cost in terms of making it generally available to a large population. Presumably, if you're in a position of advocacy and advice to sponsors, you should give them a fair chance and likelihood that they can make a contribution, and what would be the parameters, and those would be three that would occur to me.

DR. BORER: Let's go on to question 6. This one does require a vote. So, only voting members can vote.

Overall, candesartan reduced diastolic blood pressure by about 2 millimeters of mercury more at trough than did losartan, an effect size that would be sufficient for approval if a drug were compared with placebo.

6.1. Is this difference clinically meaningful for a comparison between two antihypertensives? Paul, why don't you give your answer first. We don't need long reasons, but a sentence might be useful if you want to give one.

DR. ARMSTRONG: Yes.

DR. BORER: Steve.

DR. NISSEN: Yes.

DR. BORER: Blase.

DR. CARABELLO: Yes.

DR. BORER: Susanna.

DR. CUNNINGHAM: Yes.

DR. BORER: Beverly.

DR. LORELL: Yes.

DR. BORER: Mike.

DR. ARTMAN: Yes.

DR. BORER: JoAnn.

DR. LINDENFELD: Yes.

DR. BORER: Tom.

DR. FLEMING: Yes.

DR. BORER: And I vote yes. It's unanimous.

6.2. Are the comparative safety data submitted by the sponsor sufficient to show that the expected reduction in cardiovascular risk would not be offset by other risks of candesartan, which was an issue that Paul was raising earlier. Again, we need a vote on this and perhaps a little bit of reasoning here, if you want to give some. Paul.

DR. ARMSTRONG: I would say that the data and the references and the body of information would lead me to answer that question yes.

DR. BORER: Steve.

DR. NISSEN: Yes.

DR. BORER: Blase.

DR. CARABELLO: Yes.

DR. BORER: Susanna.

DR. CUNNINGHAM: Yes.

DR. BORER: Beverly.

DR. LORELL: Yes.

DR. BORER: Mike.

DR. ARTMAN: Yes.

DR. BORER: JoAnn.

DR. LINDENFELD: Yes.

DR. BORER: Tom.

DR. FLEMING: I have some difficulty here because the data are so limited as it relates to being able to identify relative occurrences of more serious events. There are twice as many SAEs, but they are fairly infrequent in their occurrence. If one, though, looks at a broader experience for agents in this class and is able to, in essence, infer from that a favorable safety profile, then in that context I could agree as yes.

DR. BORER: And I would vote yes, but for the record I want to echo what Tom has said. I think that in voting yes, I'm voting in part on the basis of long experience with drugs in this class that make me reasonably sanguine, although I don't think there are enough safety data in this NDA to make a direct comparison. But with that caveat, I would vote yes.

6.3. Would your answer regarding the need for

comparative safety data be different if the two drugs were from different classes? For this we don't need a vote, but we do need some opinions.

Paul.

DR. ARMSTRONG: Well, most assuredly yes. I think that we know that lowering blood pressure may lead in some circumstances to favorable outcomes and in other situations the target organ and other issues may behave differently. So, I think we need clearly to look differently across classes.

DR. BORER: Tom, do you have any thoughts about this particular issue?

DR. PICKERING: I would agree with that.

DR. BORER: Are there any dissenting opinions?

DR. NISSEN: I just want to amplify on this a little bit and say that I would actually put the standard even differently for both safety and efficacy because it's all interwoven here. While I agree with what you said earlier, Bob, that in general drugs that lower blood pressure by more are generally better, but in fact we do know that there are better rather big differences between classes in the response of lowering that blood pressure for specific endpoints.

There are some data, which we'll learn a lot more from, from ALLHAT, for example, that may suggest that

calcium channel blockers lower stroke risk more effectively than ACE inhibitors and that heart failure is more effectively prevented by ACE inhibitors than calcium channel blockers. These are examples, but the point here being that without very robust data on those endpoints, small differences in blood pressure can't really be effectively described for the clinician in a way that's really fair. So, I think this really does apply to intraclass not interclass differences.

DR. TEMPLE: Let me be sure we understand. That in some sense says unless you're prepared to do an ALLHAT-sized study, you really can't get blood pressure claims across classes. I can see that as a general view, but what about the question of whether some drugs are more effective at lowering blood pressure in a black population? That might be informative. Would that mean the difference has to be larger than here, or is that just not worth even thinking about?

DR. NISSEN: That's what I was really saying there is that we said earlier that 2 millimeters is enough between two drugs in a class, that we're comfortable. I would not necessarily be comfortable in saying that drug X which was a diuretic and drug Y which was an ACE inhibitor, that there was a difference in comparative efficacy when there's only a 2 millimeter difference because I really

wouldn't know how much that 2 millimeters translated into differences in clinically relevant endpoints across two different classes. I think we could mislead clinicians if we did that. People might say, okay, it's more effective. I want to give this drug. And in fact the opposite effect would be seen on the clinically relevant endpoint, and we'd be misleading people about what the real benefits are.

DR. BORER: I'd like to offer a slightly different opinion just so that it's on the record for your edification. I think everything Steve says is very important, and certainly from John Lara and from Tom Pickering, I've gained a healthy appreciation for the potential importance of mechanism-specific therapy if you happen to know the mechanism.

But the data that we have thus far suggests -- and Dr. Kannel showed them -- that if you lower blood pressure, you're less likely to have certain problems than if you don't do it, particularly in people whose blood pressure is high. And the approvability of a single drug, before we get to the comparison of two drugs, is based on demonstration of effectiveness and acceptable safety for the intended use. So, we start out with that information about risk and benefit for the individual drugs.

Now we're comparing two drugs. It seems to me that while everything Steve says may well be true -- and in

fact, my bias is that it probably is. There are some drugs that do better at some things than others and alter pathophysiological processes differently -- we don't have those data yet. And until we do, in terms of outcomes, I think that if one drug lowers blood pressure more than another drug beyond 2 millimeters, or whatever the standard is we want to set, then based on the epidemiological data that we've heard and that have been published for years, unless there's a relative safety concern of one drug versus the other, that it's reasonable to entertain a superiority claim for lowering blood pressure. That doesn't mean that it's not important to look for the outcome events and to modify everything I've said once we get those data in hand. But we don't have them now.

As Tom pointed out earlier, based on putative mechanisms, interaction of genetics and mechanisms, interactions of gene expression in drugs and what have you, to make a guess about what we think is going to happen I think is very treacherous, very dangerous, and we shouldn't do it.

So, I would say that it's reasonable to give a comparator claim here in 6.3, assuming that the safety database is sufficient so that you can be reasonably certain that you're not adding some other risk by getting the blood pressure lowering.

Are there any other comments or questions about this?

DR. NISSEN: I just want to take the moment to challenge you a little bit, Jeff, and say that imagine a drug that produces profound reductions in blood pressure but a tremendous amount of reflex tachycardia, and now you're comparing it. They come in and they say to the agency, we want a superiority claim for blood pressure reduction, and there's no comparative data that suggests that that reflex tachycardia is really bad, but we have a bias that it probably is bad. I think we could really give the wrong advice to clinicians. Or a ganglionic blocker that reduces blood pressure very effectively but causes people to get syncopal.

So, I think we've got to be awfully careful when we compare across classes because there are unexpected effects, via the physiological mechanism of blood pressure lowering, that are not factored into the decision. So, the bar has to get raised a lot higher when you try to do this across classes.

DR. TEMPLE: And you'd certainly, I assume, be much more attentive to differences in the basic side effect profile because they're fundamentally different drugs.

DR. NISSEN: Yes.

DR. TEMPLE: And you'd need to take that into

account at a minimum, if you did it at all.

DR. NISSEN: You bet.

DR. BORER: Beverly.

DR. LORELL: I think that the example that Dr. Carabello brought up earlier of comparing hydralazine and beta-blocker is a very important one. So, I think that as question 6.3 is explicitly worded, would the need for comparative safety data be different, the answer is definitely yes. One might require a study of longer duration in a larger number of patients to be able to tease out differences in safety that might not have been seen in the size of study we're looking at today within a class.

DR. BORER: Blase.

DR. CARABELLO: Just a comment that we certainly couldn't resolve now. I think the whole issue really is what is the label. What is the purpose of the label? Is this an educational tool by which we are trying to teach the people that use the pharmacologic agent about it, or is it a marketing tool for the sponsor? I think the answer is a little bit of both.

And how far do we want to go with this? I myself would like to see the labels be more of an educational tool, but as I say, I think we could easily be here until next month on this issue.

DR. LINDENFELD: Jeff, just to add to what's

been said, I think there's a little bit of an even more middle position that that. I think there's a difference between a drug like hydralazine where we have no outcomes for the treatment of hypertension from a class like diuretics or calcium blockers where we do know that lowering blood pressure improves outcome. So, I think we'd all be very concerned about a drug that raised heart rate 14 beats where we had no outcome data at all from drug classes where we know there is a correlation between the reduction in blood pressure and outcomes data.

DR. BORER: Yes, I think that's quite right. Of course, the approval process requires that experienced regulators look at these data and raise concerns and that committees like this voice their concerns so that if potentially important tachycardia were seen, I think that a number of red flags would be raised. But what I was suggesting was the principle that if there are no safety data from a reasonable safety database that Beverly has outlined, if there are no safety data to suggest a problem that better blood pressure lowering in drugs across classes is a reasonable basis for a claim.

DR. TEMPLE: Actually one can particularly imagine differential effects on systolic blood pressure across classes. We haven't gotten that yet, but there are certainly suggestions that there might be.

DR. BORER: Let's move on.

DR. FLEMING: Can I just add?

DR. BORER: I'm sorry. Tom.

DR. FLEMING: Jeff, just a brief addition. I endorse the concerns that have been stated about caution that would need to be taken, when we're looking at different classes, particularly if there's reason to suspect that there could be a different safety profile.

In fact, I also have that caution from efficacy. My answer, for example, on question 6.1 as yes is specific only to these two agents being tested from within the same class.

DR. BORER: Let's go on to 6.4 Is the comparison between candesartan and losartan fair, as defined by ICH E-10? The relevant section is on page 7 of the document.

Paul, why don't you go ahead.

DR. ARMSTRONG: The question doesn't ask whether it was the best or the right test, but whether it was a fair test. And fairness isn't a dichotomous variable. But in reflecting on this and on the definition of fairness, we're asked to consider issues around dose, around the population studied and around the selection in timing of endpoints, all germane to the current dialogue.

I would grade this about 3 out of 4 on my

fairness test in relationship to the issues. I think it was a sensible and reasonable population.

I have some reservations about the doses. I'm convinced that 16 of candesartan is better than 50 of losartan, and 32 is better than 100. I'm not sure that 16 is better than 32 or 100 is better than 50, however. So, in looking at all of the data, I would probably have redesigned it a little differently in terms of the candesartan piece, but that's en passant.

The other issue is the duration of effect and the timing of the up-titration that I reflected on in my earlier questions. I think the timing would have been and could have been different and we could have been clearer about what dose to use and when to up-titrate, and we'll come back to that discussion in relationship to the actual wording of the label, assuming that we want to educate practitioners as to how to use these agents wisely. So, on balance, I think it was a pretty fair test.

DR. BORER: Is there anyone around the table who does not think it meets the fairness criteria that are laid out in the document? No.

Tom.

DR. FLEMING: I agree with Paul. This isn't simply yes/no. I strongly endorse the spirit of the ICH E-10 guideline on page 8, section (a), pointing out that

there really are merits to understanding, when one is looking at superiority, comparisons at multiple doses. My own sense is there's a fairness here as long as one conditions on what it is that we're claiming here. If we're claiming that we're comparing q.d. and q.d., there's a fairness here. But if one is trying to go beyond that and, in a sense, say we have established superiority to another agent relative to what its optimal efficacy might be, then I think there's uncertainty here. As I've already indicated earlier, it seems to me it would have been more informative, since we're doing two trials, in the spirit of ICH E-10, that the two trials could have differed in the way the losartan was delivered.

There seems to be more evidence that candesartan b.i.d. may not be more effective than candesartan q.d., but the data that's presented to us, though limited, suggests that there may well be a response increase with b.i.d. over q.d. I think we would have had a more informative answer, rather than two small, identically designed trials, to have taken the full benefit of doing two trials here and had the second trial look at a b.i.d.

DR. BORER: Any other elaborations on this issue?

(No response.)

DR. BORER: If not. Let's move on to number 7,

and I'd like to break this into two parts, if I may, so they don't get confounded in discussion.

First, do you recommend approval of candesartan for superior antihypertensive efficacy when compared with losartan? And forget about how the labeling might have to limit that. Let's go through that first, and then if we do agree with that, obviously the label, as everyone has said, has to be carefully constructed. And we'll talk about the labeling construction as a separate issue. So, forgetting for a moment that we have to be careful in writing a label, do you recommend approval of candesartan for superior antihypertensive efficacy when compared with losartan?

Paul.

DR. ARMSTRONG: Yes.

DR. BORER: Steve.

DR. NISSEN: Yes.

DR. BORER: Blase.

DR. CARABELLO: Yes.

DR. BORER: Susanna.

DR. CUNNINGHAM: Yes.

DR. BORER: Beverly.

DR. LORELL: Yes.

DR. BORER: Mike.

DR. ARTMAN: Yes.

DR. BORER: JoAnn.

DR. LINDENFELD: Yes.

DR. BORER: Tom.

DR. FLEMING: Yes, conditionally given that it's clear we're talking antihypertensive efficacy and we're talking at q.d. versus q.d.

DR. BORER: I vote yes too and, of course, with Tom's caveats, but we're going to get into that in a second. So, you have a unanimous vote in favor of approvability.

Now we have to talk about what it is we've actually suggested you should approve. So, if so, how should the findings of these trials be included in the approved labeling, first of candesartan? And we're going to need a vote about this. So, Paul, why don't you give the statement and we'll see if anybody disagrees and we'll vote.

DR. THROCKMORTON: Jeff, you've given the one vote that we really needed for this particular one. I'd like just discussion in general about the labels.

DR. BORER: Okay. We won't vote.

Paul.

DR. ARMSTRONG: Jeff, I'd like to make three points in terms of introducing this. The first is that for me, rather than have a discussion about a statistically significant difference with no context of what the blood

pressures were or what changes unfolded is unhelpful. To me we should dialogue or suggest to the regulatory agency that we're serving that, obviously, that be incorporated, a clinical context both from where the patients were and to what extent the difference was clinically or biologically significant as opposed to statistically significant. So, that's the first point.

The second point is I have some concerns in relationship to the draft about the notion or the implication that if a blood pressure change was not perceived to be satisfactory in the minds of the clinician caring for the patient, that he or she should up-titrate at 2 weeks. I think that that's a problem based on what we know and indeed what the sponsor has asserted in response to an earlier question. So, the notion of the appropriateness of up-titration, on the one hand, and the timing of up-titrating on the other, vis-a-vis achieving an effect, I think needs some discussion.

And the third piece is the extent to which, if one were interpreting this label, seeing a patient on losartan once a day, as to whether one should be prompted or reminded about the likelihood of increased efficacy using the same drug twice a day before switching to a new drug once a day.

So, to me those are the three issues, and I

certainly have some thoughts, but I don't want to get into the nuts and bolts of the wording. But to me those are the three issues.

DR. BORER: May I ask for a clarification here? I'm looking at the proposed addition to clinical pharmacology, clinical trials subsection from the sponsor's presentation where it says that candesartan initiated at 16 milligrams once daily and force-titrated at 2 weeks, which is the point that Paul was just making, to 32 milligrams. If I'm not mistaken, two of the most important trials, 230 and 231, the forced-titration was made at 4 weeks.

DR. FLEMING: At 2 weeks.

DR. BORER: At 2 weeks, okay. Then what was done at 4 weeks?

DR. MICHELSON: The CANDLE study was titration to effect at 4 weeks.

DR. BORER: At 4 weeks. Okay, I understand. Thank you.

Bob.

DR. TEMPLE: This is a problem. That's how the study was done, so you can't really describe it any other way. The dosing and administration says that you get most of the effect by 2 weeks and really all of it by 4 weeks. So, I think the implication is that the observing physician looks and sees if you're getting close at 2 weeks. If

you're nowhere, you maybe increase it. But it's a problem as to what to do. The real recommendation is you can expect you're not going to get any more after 4 weeks. That's what labeling has said from the beginning based on the bulk of their data.

I wanted to ask one question. We've already concluded that just saying statistically significant is not very helpful, but our immediate thought was that we'd give the numbers probably with a confidence interval and a p value. We would not have thought of saying how important and significant this is, however. Is that what you were suggesting? That's getting dicey since the whole labeling doesn't say much about that.

DR. ARMSTRONG: Sorry. Bob, what I was suggesting was that the -- and maybe you can clarify then for me. In other words, these numbers -- that is, the absolute difference between the two agents -- I thought should be reflected in the baseline values from which they occurred. In other words, the implication of those numbers might be a whole lot different in a hypertensive population that at entry came in rather different than this one.

DR. TEMPLE: That's a good addition too. It could say who the people were. Right, that's fine.

DR. BORER: Steve.

DR. NISSEN: I wanted two things added to the

label that are not in the current proposal, and they're similar to what Paul suggested. The magnitude of the change. But one of the things that troubles me about it is that clinicians may look at that and they may say, gee, 2 millimeters is trivial. A lot of clinicians don't really recognize. That in my opinion is biologically significant. So, it's going to tend to undermine the claim a little bit which I'm sure is why the sponsor didn't originally propose that. I happen to think that 2 millimeters is relevant clinically, but it may be misinterpreted. And I don't know any alternative to that. That's what I think you were probably getting at when you were saying that we think that's clinically significant, but we can't tell people that.

DR. TEMPLE: So, they could just put something in that says this is a really big deal?

(Laughter.)

DR. NISSEN: I was thinking about slightly different language than that.

DR. TEMPLE: It's a problem.

DR. NISSEN: It's a problem. It's a problem because clinicians don't necessarily get it. We want to give informative advice to clinicians. Unfortunately, it may be trivialized by some people which I'm concerned about.

Then lastly I think the way to handle the baseline issue is to describe the baseline range of blood pressures at entry. So, this was shown in people who came in between 95 and 114. Then say no more than that because I don't think we know what it is for under 95 or over 114.

So, those two additions would be helpful. But I am concerned that we not trivialize those differences, and anything you could do in the wording that doesn't undermine the clinical importance because I as a clinician, if I really -- this will change my practice, and I think that that is important when that happens. I think when I need more blood pressure reduction, I'm going to favor the more effective agent, and to me 2 millimeters or 3 millimeters is significant.

DR. BORER: Beverly.

DR. LORELL: Thank you.

I actually think the proposed label as worded is an extremely good starting point. I like it because it states the facts very clearly of the results explicitly in two trials. So, in a sense it does not have to get to the point that you were making, Dr. Armstrong, about the issue of when you up-titrate or don't.

I think it is very important in this label that it have an explicit statement as to who the study population was. This study, unfortunately, cannot be

extrapolated to patients who have isolated systolic hypertension, and I think it's very important not just that there be sort of a demographic, this is the baseline, but that it be very clear that an inclusion criteria required having diastolic hypertension.

Secondly, I think going back to the points we've discussed over and over here, we're all extremely sympathetic and hopeful that this reduction in blood pressure that was seen as the superiority claim will translate to outcome measures that are very important. But we don't know that. So, I think that probably the most straightforward approach and also as a precedent for the FDA is to simply state the facts of the trial, to have a very simple table that lists baseline blood pressure and the mean and median reduction at the 8-week endpoint. And it can be left for the clinician to interpret, as he or she sees fit, what that means.

I think to have a statement in trying either to encourage or to dissuade interpretation of that right now is very flawed because this study did not compare endpoints between the between the two drugs. We hope it will translate to endpoints, but we don't know that.

DR. BORER: Before I ask Tom Fleming to comment, because I think some of his earlier comments are crucial with regard to the response to this question, let

me ask, Beverly, would you modify those parameters you mentioned, mean, median -- and I'm sorry. I didn't hear the third one.

DR. LORELL: The baseline demographic absolute blood pressures.

DR. BORER: In addition to the mean and median change, I would suggest one might want to include either the standard deviation or the range --

DR. LORELL: Certainly.

DR. BORER: -- because even if you really didn't understand or didn't know all the epidemiological data, you would at least have a sense that sometimes you can have a fairly marked effect, and that would be reassuring.

Tom, why don't you go ahead and talk about the label.

DR. FLEMING: There were two or three aspects. The first couple have already been raised by Paul and Beverly for which I would suggest there be modifications.

First, I think it's not sufficient just to provide statistical significance as the conclusion here. I agree with Paul's point that there really needs to be explicit data indicating the essence of what the antihypertensive efficacy results are.

By doing that, we address two of my concerns.

One is that it be made very clear that what we're talking about here are 8-week results on blood pressure, and that will become explicit, and what the magnitude of these effects are, which is critical that that be conveyed beyond just statistical significance.

The third suggestion that I have or the third issue that I would like to have addressed is related to what the FDA medical reviewer raised on page 27, and that is, I think there needs to be a sense, kind of in the spirit of fairness of E-10, a sentence at the end or at some point that says that comparisons were not made against losartan b.i.d. that might be more effective as a regimen than q.d. Then it's made explicitly clear that the superiority in blood pressure effects are q.d./q.d. and yet it's acknowledging that there is not an assessment relative to b.i.d. losartan that, in fact, might be more efficacious than q.d. losartan.

DR. BORER: Can I ask for a little bit more discussion about that last point? My understanding of the data -- and correct me if I'm wrong, and Tom, maybe you can help us with this -- is that there is the sense from some of the published data that the b.i.d. dosing schedule may be more effective than the q.d. dosing schedule of losartan, and that certainly for some patients it's observably better. But are the data sufficient to make a

general statement that it is known that b.i.d. dosing of the one drug is better? And if not, is it appropriate to include a statement like that in a new label?

DR. PICKERING: Well, I think from what we've heard so far, the difference was with the 25 milligram dose but not with the 50 milligram dose from the data that we saw from the Weber study.

DR. FLEMING: Let me just clarify, Jeff, because I think you said something substantively different from what I said. I said a sentence should be added that indicates that comparisons were not made against the losartan b.i.d. schedule which may be more effective than q.d., as opposed to what I thought you said which is has established to be.

On page 14 in the FDA briefing document what we have -- and granted, it's only at the 25 dose, but we have differences of 2.2 millimeters. It's in a study of a size 100 per arm. So, that's 1.4 standard errors larger -- standard errors are 1.4 times larger than in the two pivotal studies that had 300 per arm. But those pivotal studies, relative to the primary endpoint, basically yield, if you look at 8-week results, 1.3 and 1.8 millimeter differences. So, the estimates that we're viewing on primary endpoint as evidence of efficacy, when you're comparing candesartan and losartan, are actually of smaller

magnitude than these differences q.d. versus b.i.d. within losartan. They are statistically a little bit stronger because they're based on three times the sample size, but they're only two-thirds the magnitude of effect. So, the p values are not all that different.

So, basically I'm not claiming or I'm not stating that there needs to be an acknowledgement that b.i.d. losartan is more effective than q.d., but it certainly may be. There's certainly some evidence here to suggest that it is, and that evidence is not a whole lot weaker than the evidence that we're using for the primary endpoint for the conclusion that candesartan is more effective than losartan.

DR. BORER: Beverly.

DR. LORELL: I would respectfully disagree with that opinion. I think that it is correct that losartan may be more effective, but I don't think the data is clear enough to state that explicitly in the labeling. In fact, the current labeling for losartan -- and perhaps you could clarify that for us -- uses very careful terminology of "could consider using" as opposed to making a statement "may be more effective." And those are really two very different statements.

DR. FLEMING: But let's pursue that. Are they different? I intentionally used the word "may" be to be

very cautious.

DR. LORELL: Well, I think that the statement in labeling "could consider using" is quite a different statement than "may be more effective." I think that an alternative approach could be to simply state that in the labeling as proposed, these studies did not compare b.i.d. regimens of either drug. And that makes it very clear to the practitioner who is deciding to use either drug that the comparison wasn't there. We wish it were, but it wasn't there.

DR. BORER: Yes. If we mandated a statement about this at all, I would favor Beverly's statement that says we just didn't do it, rather than drawing a conclusion about what it might be.

Steve.

DR. NISSEN: Yes. I really fairly strongly disagree here, and let me see if I can articulate it.

First of all, if you read the label, it says once daily. I mean, it's very clear that that's what's being compared when describing the studies. To me that's quite sufficient.

DR. TEMPLE: Which drug are you talking about?

DR. NISSEN: I'm talking about the candesartan. The proposed label says: compare the antihypertensive efficacy at their once-daily maximum doses. It's

absolutely crystal clear in that proposed label that's what's being said.

Look, in designing a clinical trial, you can't look at every combination and permutation of administering a drug. So, you can set the bar impossibly high here and you can kind of whittle away at it. But the comparison was fair, by the terms of my interpretation of the guidance, and I just think we don't comment on b.i.d. And frankly, the sponsor isn't suggesting saying anything about b.i.d. administration. The label says once a day.

My view here is actually colored a little bit by the fact that I wish we had more comparative trials between agents in the same class like this. If we kind of whittle away at the claim when there's a very clean pair of trials that show us the answer here, then we undermine our ability to get data like this in the future.

B.i.d. dosing wasn't studied. It would have taken another large study to actually do it, and maybe some day they will do it. But all they're commenting on in the label is once-daily maximum doses, and I think that's all we should comment on based upon the study.

DR. BORER: Beverly, did you have another comment?

DR. LORELL: I think in a sense we're on the same page, Steve. I would look at adding that labeling

simply as a bit of an added clarification for the naive reader, thinking about labeling not just as marketing, but an education tool.

DR. LINDENFELD: May I change the topic? Are we done with this one?

DR. BORER: Let me just ask, are there any other opinions different from what we've heard? You've heard a range.

I'm sorry. Tom.

DR. FLEMING: Just to follow up on Beverly's and Steve's comments, if there were no data or if the data that existed, even better yet, really provided some considerable reassurance that losartan q.d. and b.i.d. were the same, I'd be very comfortable with what you're proposing. There's not a lot of data here that were presented. What were presented on page 14 is suggesting to me magnitudes of effects that aren't a lot different than what we are seeing for candesartan against losartan. But maybe there's a lot more to it than what these data are showing.

So, what is the committee's sense about is it your belief that these data on page 14 that are showing a 2.2 millimeter difference are entirely misleading and this is irrelevant? And essentially you have the strong sense that there really isn't a difference, in which case then I

understand your recommendation.

DR. LORELL: If I could respond to that. I would say that they raise an hypothesis that we all wish had been more rigorously tested. I think that my rationale -- and I want to be clear about this -- for adding a very straightforward comment that b.i.d. dosing was not tested relates more to the current labeling of the drugs as isolated agents where the clinician is given the option of using b.i.d. So, I think your concern is a very fair one. I think we'd all love to see another trial done to address that, but we just don't know.

DR. ARMSTRONG: Perhaps another way of coming at this, Jeff, would be to find out from the sponsor, since the label currently for candesartan lists b.i.d. as an option for the new agent, as to whether we're equally unclear about the efficacy of b.i.d. candesartan as we are b.i.d. losartan.

DR. BORER: They showed us the data. Well, why don't you go ahead and answer.

DR. MICHELSON: To address that first piece, yes, we have the same limited data that you saw, very limited and not sufficient to answer other than there appears to be small differences with each of the agents.

I would point out just one thing, if I may, just to Dr. Fleming. I could tell you there's been a

commitment by both the manufacturers of losartan and to us in every large outcome study that's either ongoing, completed, or to be done with each of these agents is employing only the once-daily dosing either, for example, losartan 50 milligrams once daily or 100 milligrams once daily, and the same for us. All the outcomes trials we have basically are including either 16 or 32 milligrams once daily so that all the outcomes data that you're going to see and have seen, in fact, such as RENAAL and others will employ that dosing. So, that will also make it even more relevant.

DR. BORER: I haven't stated my opinion about this, but I will, if I may. I don't think it's necessary to include a statement about b.i.d. dosing in the label. But if the sense was that one needed to, I would do what Beverly suggested, just state that it wasn't studied.

In terms of Tom's point, because he asked a question, I'm not persuaded by the data on page 14. The number of patients involved was relatively small so that my confidence in the absolute values, the absolute changes is not overwhelming. There's a wide confidence interval.

The populations were sufficiently small so that I certainly don't infer immediately that the population involved here was the same as the population or superimposable upon the populations that were studied in

230 and 231.

In addition, as Tom pointed out, this is 25 b.i.d. It's very hard for me, without a direct comparison, to draw inferences about how those results would compare with 100 q.d. of losartan or 32 milligrams q.d. of candesartan, or what have you.

So, I think those are interesting data. They raise questions. As Beverly says, they're hypothesis-generating. But I'm not influenced in my conclusion about what to put in this label by those data. Now, that may be wrong, but that's the way I would respond to the question.

Are there any other comments about this issue? I'm sorry. Tom, if you would turn on your light, I'll see you every time.

DR. FLEMING: Just a very brief added comment. If the FDA, in fact, gains access to additional data beyond what's on page 14 that provides additional substantive insight and if that in fact suggests that there's less gradient here between b.i.d. and q.d., then I'm entirely comfortable with what Steve has proposed as not adding any statements.

On the other hand, if we're essentially looking at this evidence, I would consider Beverly's proposal as kind of a compromise middle ground from what I had proposed as a very acceptable alternative.

DR. TEMPLE: I said this before, but nobody seemed impressed. Let me try again.

The fact that you see the same differences at peak, it seems to me, has a lot to do with how worried one should be because the reason you use b.i.d. for some drugs is that you think their half-life is too short. But you do expect that the dose, when you first take it, will probably get into the right range. Even in that circumstance, where the two were compared at doses that really should have been adequate, there was a difference at peak, suggesting that it's not just a matter of half-life and timing, but maybe something else.

DR. NISSEN: That was also part of my thinking as well, and also, Bob, the fact b.i.d. candesartan appears to have a little bit bigger effect than q.d. candesartan. So, Tom, the reason that I think we've got to be careful here is that if you did b.i.d. candesartan against b.i.d. losartan, I think there's every reason to expect you'd see the same differentials because both drugs show a little bit more efficacy when given b.i.d. So, to me it's just kind of a nonissue.

DR. BORER: Let's move on to the issue of the implications for labeling of losartan. Paul.

DR. ARMSTRONG: I don't see any implication for losartan labeling. So, no.

DR. BORER: Is there anyone around the committee who would suggest any changes in the losartan label based on these studies? JoAnn.

DR. LINDENFELD: No.

But I just wanted to come back to one point earlier in the labeling. I don't know if this troubles anyone else, but if you do put the numbers of actual blood pressure, I'd like to see the numbers for the lower dose of each drug, 16 and 50, because that's where almost all of the difference is. Now, we could argue about whether or not that's fair. That was not the endpoint of the study, but there was, I think, on page 18 of the briefing booklet a suggestion for a phrase that might indicate that. I think it would be helpful to the physician using these drugs to know what the increments of effect are as you go up on the dose. You get almost all of it early. I think that would be helpful data to have in there.

DR. BORER: We're not suggesting any changes for the losartan label.

Finally, 7.3. Do we suggest any implications of these findings for combination products containing either of these two drugs, candesartan or losartan?

Paul.

DR. ARMSTRONG: I'd have to take them one at a time. I would say that there may well be implications and

each would need to be addressed on its own merit.

DR. BORER: Specifically with regard to candesartan, how would you suggest these results should be used?

DR. ARMSTRONG: Sorry. Are we talking about candesartan combined with something else?

DR. BORER: Yes, a combination with a diuretic or something.

DR. THROCKMORTON: Candesartan with a thiazide or CCB or something.

DR. ARMSTRONG: I would say it hasn't been studied.

DR. BORER: Blase.

DR. CARABELLO: Yes. You couldn't possibly make a statement about superiority of this drug when mixed with something else. It could entirely disappear. We couldn't possibly be justified in adding that to the label of essentially another drug.

DR. BORER: Does anybody around the table disagree with that? Beverly.

DR. LORELL: I strongly agree.

DR. BORER: We have a strong agreement and other degrees of agreement.

DR. THROCKMORTON: Sense of committee so noted.

DR. BORER: I think that that concludes our

business, but I would like to ask one final question just for the edification of the committee, if nobody else. A precedent was noted here with regard to an angiotensin-converting enzyme inhibitor that's marketed by two different companies. I am not aware that studies similar to this one were performed with that drug and its comparators, and I'd like to know the basis of the labeling that was quoted here. Can you tell us a little bit about that?

DR. THROCKMORTON: Can you give me a page number?

DR. BORER: Yes.

DR. NISSEN: It's CR-12 in the AstraZeneca presentation.

DR. MICHELSON: Would you like to see the study design?

DR. BORER: Sure. Well, I'd be interested to see the study design, sure. It may be obvious why the labels were written.

DR. TEMPLE: I'll tell you what. It was probably a brain spasm.

(Laughter.)

DR. TEMPLE: We were trying to think more about giving people some idea what the ball park was. So, for a number of drugs, we said this is in the general range of

most ACE inhibitors or this is in the range. That's really what that reflects. Is it a non-inferiority study with a margin calculated? Absolutely not. It's well short of that. What it says is this looks like one of those, and that's all it is. We've sort of stopped doing it because it's really hard to justify. But there was some desire to say, well, you know, don't be confused. This is another one of those. That's what it is. We're not necessarily proud of it.

(Laughter.)

DR. BORER: So clarified. I would like to suggest, for whatever it's worth -- and I don't think anybody on the committee will disagree -- that the principles in ICH E-10 here ought to be more rigorously applied before the label is written again.

Are there any other comments from the committee?

DR. FLEMING: Jeff, we had deferred just a few additional comments on question 4. Is this timely to return to that?

DR. BORER: Sure, why don't we take a few minutes and get some comments about that.

DR. FLEMING: Let me try to be really brief in clarifying at least what I was trying to suggest we would need to state in response in particular to question 4.1.

Let me give three scenarios.

The first scenario is you have a comparator agent that has shown a blood pressure effect and ultimately has a clinical endpoint study that's directly shown effects on stroke reduction. Now, your experimental agent in comparison to the comparator has been shown to be superior in blood pressure effects, and that's all that you know. But there's no reason to expect that it doesn't contain all of the other mechanisms in this particular scenario. Then I would think that the comparator agent would be labeled for not only blood pressure control, but actually having documented that it prevents stroke, whereas the experimental agent in this case could be called superior in its antihypertensive efficacy. I don't think you'd have to explain what isn't known because there's no specific evidence that it doesn't provide the benefits, but you're not making a claim for it having established effect on stroke.

Scenario B is a scenario where the comparator agent has had clinical endpoint studies and there's considerable evidence to show that its effects on clinical endpoints exceed that that you would expect to be mediated through blood pressure reduction. In this setting then, if you have done a comparative study of the experimental agent and showed a superior antihypertensive effect, you can

claim a superior antihypertensive effect. But what I was saying is I would think there has to be an acknowledgement, though, that the comparator agent has achieved clinical benefits in ways that would exceed what you expect to be mediated through blood pressure lowering.

The third scenario would be one where you actually have the experimental agent showing a superior antihypertensive effect, but you actually have clinical endpoints on both and the comparator is superior in clinical endpoints. In that setting, I would think without question the focus has to be on the clinical endpoints and you wouldn't be even talking about a label that would talk about superiority in antihypertensive effects.

Those are sort of the cascading three separate scenarios that kind of cover the possible options. This was what I was trying to argue before we would need to report.

DR. BORER: Paul, did you have a comment?

DR. ARMSTRONG: Just on point three, there will be circumstances, Tom, it seems to me, when benefits of an agent are largely a function of the participation in the clinical trial and the rigor, discipline, and monitoring associated with it as opposed to clinical practice, and the issues of efficiency and efficacy come to mind, of course. So, I think in approving a new drug, one needs to take into

account not only the evidence for efficacy in a clinical trial, the safety, the compliance issues, and the cost, but the general applicability. So, I would have some sympathy as a clinician to keeping an open mind, notwithstanding the fact that the points you raise are good discussion points as we take each new customer who comes to the table.

DR. BORER: I think the principles that Tom has stated are important for the FDA to consider. Obviously, they're going to have to be considered in the context of specific data sets and specific trial designs, and you can take that advice.

With that having been said, why don't we adjourn for the moment. We have 46 minutes and 48 seconds before we will reconvene.

(Whereupon, at 12:13 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:03 p.m.)

DR. BORER: We'll begin very slowly so that our stragglers can come back.

The committee is composed of the same people that were introduced this morning. In the interest of complete disclosure, we'll introduce ourselves again. Tom.

DR. PICKERING: I'm Tom Pickering from Mount Sinai Medical Center in New York.

DR. CUNNINGHAM: Susanna Cunningham from the University of Washington in Seattle.

DR. CARABELLO: Blase Carabello from the Baylor College of Medicine.

DR. NISSEN: Steve Nissen with the Department of Cardiovascular Medicine at the Cleveland Clinic School of Medicine.

DR. ARMSTRONG: Paul Armstrong from the University of Alberta.

DR. BORER: I'm Jeff Borer. I'm from the Weill Medical College of Cornell University. This morning I slipped and said Cornell Medical College. That should be corrected.

MS. PETERSON: I'm Jayne Peterson. I'm the acting Executive Secretary of the committee.

DR. FLEMING: Tom Fleming, University of

Washington, Seattle.

DR. LINDENFELD: JoAnn Lindenfeld, University of Colorado.

DR. LORELL: I'm Beverly Lorell, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston.

DR. THROCKMORTON: Doug Throckmorton, Director of the Cardio-Renal Division, FDA.

DR. TEMPLE: Bob Temple, Director, ODE I.

DR. BORER: Jayne Peterson will read the conflict of interest statement.

MS. PETERSON: Thank you.

The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Dr. JoAnn Lindenfeld has been granted a waiver under 18 U.S.C. 208(b)(3) for her potential consulting for

the sponsor of Pravagard on unrelated matters. Potentially she could receive less than $10,001 from this firm per year.

Also, Dr. Jeffrey Borer has been granted a waiver under 18 U.S.C. 208(b)(3) for his potential consulting for the sponsor of Pravagard on unrelated matters. Potentially he could receive less than $10,001 per year.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

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

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. BORER: Thank you, and for completeness, our final committee member will introduce himself.

DR. ARTMAN: I'm late.

(Laughter.)

DR. ARTMAN: I apologize. I'm Mike Artman. I'm at New York University School of Medicine.

DR. BORER: This afternoon we're going to consider the NDA for the pravastatin-aspirin combination product that was considered initially at an earlier meeting. Some additional information is going to be presented by the sponsor and we'll start with Dr. Baumgartner.

DR. BAUMGARTNER: Thank you, Mr. Chairman. Good afternoon. My name is Tom Baumgartner. I'm Vice President of Regulatory Sciences for Bristol-Myers Squibb. We market pravastatin and buffered aspirin.

We're here before you today as you reconsider our NDA for a combination product consisting of our lipid-lowering agent pravastatin, along with aspirin, for use in the setting of secondary prevention in patients with established coronary artery disease.

As you know, both these agents are approved by the FDA to reduce the incidence of clinical cardiovascular events in the secondary prevention population and also are recommended as cornerstone of therapy in secondary prevention by the American College of Cardiology and the American Heart Association in their treatment guidelines.

I'd like to recap for the committee the chronology of events which have led us to come before you again today. As part of this, I will also frame what are the issues we've been asked specifically to focus on today.

Bristol-Myers Squibb originally submitted an NDA for this combination product in June of 2001. The basis for this application was a meta-analysis of five pravastatin cardiovascular event trials in patients with established coronary artery disease. The application was reviewed by this committee at its January 2002 meeting where numerous issues were discussed.

Since that time we've worked closely with the FDA to try to clearly define what were the remaining issues to be resolved to allow for the approval of this product. Based on these interactions, we revised our application to address these outstanding issues, and the application was refiled in May, which has led us to come before you today.

The core of the original application consisted of the meta-analysis of five pravastatin cardiovascular event reduction trials which demonstrated that the combination of pravastatin plus aspirin was safe and effective and that the combination provided added benefit over both pravastatin and aspirin when given alone in the prevention of subsequent cardiovascular events in patients with existing coronary heart disease. Following my

presentation, Dr. Rene Belder of our Metabolics Clinical Research Group will briefly review these analyses for you.

In addition to the meta-analysis, the original NDA also included a pharmacokinetic study which demonstrated that there were no pharmacokinetic interactions when the two drugs were given together.

When this application was reviewed by this committee in January, many issues were discussed. As noted by FDA in the prologue for today's questions for the meeting, at the time of the January meeting, there appeared to be several areas of the application where general agreement had been reached.

First, it appeared that there was general agreement that there was indeed a population which could be identified for which this combination product would be indicated.

In addition, it was generally agreed that the meta-analysis demonstrated the safety and efficacy of the combination, as well as the independent contribution of the components, to the beneficial cardiovascular outcomes in the secondary prevention population.

Finally, the choice of aspirin doses to be offered appeared to be acceptable to the committee.

While there appeared to be general agreement on some aspects of the application, other issues remained

outstanding. We feel we have addressed these issues in the refiled NDA, including the briefing book which was distributed for today's meeting. For today's presentation, we will be focusing on four of these issues as were outlined by the FDA in their prologue to the questions for today.

In his presentation, Dr. Rene Belder will address issues raised by the committee in January regarding the range of pravastatin doses to be available for this combination product.

In addition, he will address aspects related to the safe use of aspirin, considering that it now will be a component of a prescription combination product. This will include a discussion of the features of this product which we feel may, in fact, reduce the risk for the inadvertent use of aspirin in settings where it might not be desirable, such as in surgery. In addition, he will address the implications and risks for bleeding should aspirin not be discontinued prior to surgery.

Dr. Belder also will discuss the potential for inappropriate discontinuation of pravastatin during times when it might be desired to temporarily interrupt this product owing to its aspirin component.

In the next few minutes, I'd like to address the final bullet on this slide, which is the concern over

the potential for inappropriate use of this product in a non-indicated population such as in primary prevention.

In addressing this concern, first I'd like to reemphasize that the indication we are seeking and the only indication which we plan to promote is for the reduction of the risk of clinical cardiovascular events in the secondary prevention population. This is a use in a population for which both aspirin and pravastatin already are approved by FDA.

As shown on this slide, we have proposed an intersection label for this combination product. By that I mean a label which we feel reflects a population where the secondary prevention claims in both the aspirin and pravastatin labels intersect. The proposed indication provides for a medication that allows for and enhances long-term management to reduce the risk of cardiovascular events in patients with clinically evident coronary heart disease.

Regarding the potential for off-label use of this product in primary prevention, the reality is that in the current practice environment with aspirin available over the counter, aspirin is currently being used in primary prevention. However, we do not feel that the availability of this combination product will increase the likelihood of off-label use of aspirin over what currently

exists with aspirin being available over the counter. Rather, the fact that the pravastatin-aspirin combination will be a prescription product should actually allow prescribers to have greater control over ensuring that these drugs are used in the appropriate population.

In support of our refiled application and our presentation, we have brought some of the world's experts on the topics to be discussed today who are available to us, as well as to the committee, for the discussion. These consultants include: Dr. Jerry Avorn, a pharmacoepidemiologist from Harvard, who authored the literature review on the risk of aspirin use during surgery which was provided as part of the briefing book for the meeting today; Dr. Don Berry from M.D. Anderson who worked with us on the meta-analysis for the original submission; Dr. Bernard Chaitman from St. Louis University who is an author on the ACC/AHA guidelines on perioperative noncardiac surgery; Dr. Lawrence Dacey who is a cardiothoracic surgeon from Dartmouth who has published on the perioperative use of aspirin in cardiac surgery. Dr. Charlie Hennekens from Miami has extensive experience on the use of aspirin in secondary prevention and submitted a citizens' petition for aspirin to be approved in secondary prevention which was approved by the FDA in 1998. Dr. Tom Pearson from Rochester is a preventive cardiologist. Dr.

Marc Pfeffer from Brigham and Women's Hospital who was an investigator on the pravastatin CARE study, and Dr. Eric Topol, Chair of Cardiovascular Medicine at the Cleveland Clinic, who is an expert on antiplatelet therapy in cardiovascular disease.

The agenda for our presentations for this afternoon is as follows. Following my remarks, Dr. Rene Belder from our Metabolics Clinical Research Group will review the contents of our refiled NDA and address the issues I noted previously regarding the pravastatin doses which are now to be offered in the combination, safety aspects related to the aspirin component of the product, and temporary discontinuation of statin therapy. Dr. Fred Fiedorek, also of our Metabolics Clinical Research Group, will conclude by summarizing our application and by providing the regulatory context and rationale for this product.

I'd like to introduce Dr. Rene Belder, Executive Director of Clinical Design and Evaluation for Metabolics from Bristol-Myers Squibb. Thank you.

DR. BORER: Are there any questions for Dr. Baumgartner at this point, or are we all set to move on?

(No response.)

DR. BORER: Okay, let's move ahead then.

DR. BELDER: Good afternoon, ladies and

gentlemen. I'm very happy to be back here today to present to you the features of our refiled pravastatin-aspirin application.

To give a top line overview, cardiovascular disease remains the leading cause of death in the United States. However, we also know that both pravastatin and aspirin are approved medications for use in the secondary prevention population. The pravastatin-aspirin combination will, therefore, provide a useful tool for both health care providers, as well as patients, to prevent coronary artery disease.

As Tom already indicated, I will give you a brief summary of the data that we presented last January for those of you who were not here at that time.

The efficacy and safety of the pravastatin-aspirin combination was based on a meta-analysis of five pravastatin prevention trials. These trials are listed here on this slide. All trials randomized pravastatin 40 milligrams and placebo. All trials had as a prespecified endpoint cardiovascular events, and in total there were about 15,000 patients randomized to either pravastatin or placebo. The largest contribution came from the CARE and the LIPID study that provided about 98 percent of the total patient-years of exposure, which was almost 80,000 patient-years. In addition, you can see that about 80 percent of

these patients were also taking aspirin.

The results of the meta-analysis are presented here on this slide for three endpoints considered of most importance for this combination product, namely fatal or nonfatal MI, ischemic stroke, and the combination of coronary heart disease death, nonfatal MI, ischemic stroke, or revascularization procedures. For both comparisons, namely the combination of pravastatin and aspirin versus aspirin alone, indicated here in yellow, as well as the comparison between pravastatin and aspirin versus pravastatin alone, for all these comparisons there was a significant benefit of the combination over the individual components.

In addition, we examined the safety of pravastatin and aspirin when used together in these trials, and we did not find any sign of an increased incidence of CK or liver function test abnormalities or gastrointestinal bleeds or hemorrhagic stroke, obviously all events of interest for these products.

Let me now move on to the topics I've been asked to discuss with you today.

First of all, the choice of pravastatin doses to be provided in this combination product. Last January we presented to you the rationale of a combination product of 40 milligrams of pravastatin with either an 81 milligram

dose of aspirin or a 325 milligram dose of aspirin. The 40 milligram dose of pravastatin was chosen because that's currently the approved starting dose of pravastatin. In addition, the 40 milligram dose was used as a starting dose and maintenance dose in all prevention studies with pravastatin.

The committee, however, felt that a greater flexibility in the dosing with regard to pravastatin was desirable, and we're therefore now also offering the 80 milligram dose of pravastatin for those physicians who like to see greater cholesterol reductions in their patients, as well as the 20 milligram dose of pravastatin, which is provided for physicians who are taking care of patients with renal or hepatic impairment or patients who are also using immunosuppressive therapy.

I'll now move on to the potential of excessive bleeding should the pravastatin combination not be discontinued prior to surgery, and this aspect is divided into two topics. The first one is the potential of inadvertent continuation of aspirin with this prescription combination product, and the other aspect is if aspirin is continued during surgery, what is the risk associated with its use. Let's start with the first part.

In order to understand the risk of inadvertent use of aspirin, we first have to understand what is the

current situation with respect to over-the-counter use of aspirin for secondary prevention. The current situation is characterized by ambiguity for both health care providers as well as patients primarily because there are many OTC aspirin-only products available from which the consumer has to make a selection for secondary prevention. You see some of these products here on this slide. In addition to these products, there are also numerous generic aspirin products available. Also, you can see that the doses available of these products of up to 650 milligrams would not be desirable for secondary prevention.

Secondly, there are many over-the-counter products available that contain, in addition to aspirin, other active ingredients, some of which may not be appropriate for patients with coronary heart disease. And these are the products that are available for the consumer to choose from of products that contain aspirin. I would also like to mention that these products may actually contribute to inadvertent use of aspirin prior to surgery because many patients or even physicians may not realize that one of the active ingredients of these products indeed is aspirin.

Lastly there are also OTC products available that can be confused by a consumer as aspirin substitutes, and it was indeed shown here by a study from Cook from Dr.

Hennekens' group that showed that of those patients who were thinking that they were taking aspirin for secondary prevention correctly, actually 15 percent came home with aspirin substitutes, such as acetaminophen. In addition, of note is that in this study in a general population, only 51 percent of those patients who should have been taking aspirin for secondary prevention were actually taking it.

These are the products that can easily be confused by a consumer as aspirin equivalents and products that do actually not provide the benefit in secondary prevention.

It may, therefore, be clear that the prescription use of aspirin in this combination product may actually offer some advantages. Physicians will be better able to ensure that aspirin is used rather than a substitute and will also be able to select a dose that is most appropriate for secondary prevention. In addition, we believe that other physicians will be better able to recognize that aspirin was used as part of a prescription product and recommend discontinuation or continuation as appropriate.

Of course, it is important that both physicians and patients are aware of the aspirin component of this product, and we have, therefore, developed labeling that clearly indicates the aspirin component of this product.

This is the example of the proposed package showing the aspirin component indicated four times. In addition, we have developed a patient information leaflet also clearly indicating that this product does contain, indeed, aspirin.

I'll now move on with what is the risk if aspirin is, indeed, continued during surgery. What is the risk of excessive bleeding?

Aspirin has been studied in noncardiac patients in several surgical settings, and the results of these studies are summarized on this slide.

First of all, aspirin has been studied in vascular surgery to prevent graft occlusion, and the results here are of a meta-analysis performed by the Oxford Group.

In addition, aspirin has been studied in patients at high risk for venous thrombosis and pulmonary embolism, and that's the middle study presented here on this slide.

And finally, there was a large prospective study of aspirin in patients undergoing hip surgery also to prevent pulmonary embolism. In this study, aspirin was started 7 days prior to surgery.

When we look at the safety of aspirin used during surgery in these studies, we see that there was no large excess of bleeding and there was no increase of fatal

bleeds associated with its use. Indeed, aspirin prevented graft occlusions and prevented pulmonary embolism. So, there was an overall benefit of aspirin in this setting.

Aspirin has also been studied in several studies in patients undergoing coronary bypass procedures. Of note is that the earlier studies indeed show that there was an increased need for transfusions and an increased need for reoperation for bleeding. However, the more recent studies do not observe this same finding, and there's actually a hint of a possible benefit when aspirin is used during surgery in these patients undergoing coronary bypass procedures. And I will discuss these data a little bit more.

We, therefore, believe that the concern about the inadvertent use of aspirin in surgery in patients with coronary heart disease has actually decreased over the last number of years for several reasons, and I will discuss these with you.

First of all, improved surgical procedures reduce the risk of bleeding complications. This is data from a study from Dr. Dacey's group, and as indicated, Dr. Dacey is here today. If you look at the last observational period on this slide, indicated here -- and this is data from over 12,000 coronary bypass procedures performed in northern New England -- you see that the rate of re-

exploration due to bleeding is actually decreased, while during this same period of time, the use of aspirin in these procedures has actually dramatically increased from 22 to 78 percent. This effect is mainly attributed to improved surgical techniques and procedures, as well as improvements in hemostatic measures.

As I indicated before, there may even be some indication of a potential benefit with respect to the use of aspirin in this particular setting, patients undergoing bypass procedures. Again, this is data from Dr. Dacey's group who showed in an observational study in over 8,000 coronary bypass procedures that there was no increased rate of re-exploration for bleeding. There was no difference in the need for blood products. However, there was a significant reduction in in-hospital mortality associated with aspirin use.

However, there's no good, well-controlled, prospective clinical data of the use of aspirin in the surgical setting in patients with coronary heart disease. Therefore, there remains a lack of consensus about what to do with aspirin in these patients, continuation or discontinuation. And that is evidenced by the ACC/AHA guidelines on the perioperative medical treatment of patients with coronary heart disease in noncardiac surgeries. These guidelines do not provide specific

recommendations about discontinuation or continuation of aspirin. One of the authors of these guidelines was Dr. Chaitman. Dr. Chaitman is here today to comment on these recommendations.

However, most importantly, we believe that with the availability of this combination product as a prescription product, the likelihood of inadvertent continuation of aspirin is actually reduced compared to the current situation where aspirin is essentially used over the counter for a variety of reasons.

The last topic to be discussed today is the potential for inappropriate continuation of pravastatin, again in a setting where, for instance, this combination product would be discontinued, if needed, before surgery.

First of all, it's important to note that unlike aspirin, whose onset of action is very acute, with statins in general in the secondary prevention population, it takes a while before the effects from cardiovascular events become apparent. One would, therefore, not expect a brief interruption of statin therapy, for instance, for a couple of days before a surgery, would have any immediate adverse consequences. And indeed, there's no data pointing in that direction. However, more importantly, the individual components will remain available for the physicians to manage interruption or discontinuation of one

component and continuation of the other.

In summary, we believe that with the actions discussed today, we have addressed the main concerns. First of all, we have now made three pravastatin doses available: in addition to the 40 milligrams, also the 20 and 80 milligram doses of pravastatin. In addition, we have developed packaging and labeling that clearly identifies the aspirin component, increasing awareness by both patient and physician of the aspirin component of this product.

I would now like to hand over to Dr. Fred Fiedorek for summary comments unless there are questions.

DR. BORER: Are there any questions for Dr. Belder? Paul.

DR. ARMSTRONG: I may have missed it, but in the approximately 1 out of 5 patients not on aspirin in LIPID and CARE, were the baseline characteristics of those patients as compared to the others in those studies factored into the meta-analysis?

DR. BELDER: Yes. That was extensively discussed last January.

DR. ARMSTRONG: Okay.

DR. BORER: Any other questions? Okay, why don't we go on to Dr. Fiedorek. Oh, sorry. Steve.

DR. NISSEN: In the original application, we

were asked to consider this as if the two drugs would be together in one tablet. Has there been a withdrawal of the request for approval for a single tablet containing both compounds?

DR. BELDER: No. The prologue to the initial meeting advised you to consider this as a single tablet. And we still have a single tablet on stability. So, a single tablet will be offered as soon as we have enough stability data to launch it. At this point in time, it's a co-packaged product.

DR. NISSEN: Right. But what you said earlier was that if we wanted to discontinue the aspirin component for any reason or the statin component, we would be able to do so. But that's true only in the co-packaged product. The intent is not only to market the co-packaged product, but also the combination eventually.

DR. BELDER: Correct, yes. But what I meant is that if a physician continues the single combination tablet, but wants to continue one of the components, then he would go back to the single component use. So, it's basically back to the old situation.

DR. NISSEN: So, it really isn't a change then in what you're requesting.

DR. BELDER: Correct.

DR. BORER: Dr. Fiedorek.

DR. FLEMING: One other question.

DR. BORER: Oh, I'm sorry. Tom, go ahead.

DR. FLEMING: In the materials that the medical reviewer presented to us from FDA, there was a lot of consideration to the Nelipovitz article that set up basically models to try to address the tradeoffs between bleeding risks against reductions, for example, in MIs. Will you be giving us more information on that?

DR. BELDER: We were not intending to. We're also not making a strong argument that we think aspirin is beneficial during surgery in patients with coronary heart disease. Our primary contention is that since this is a combination prescription product, physicians should be able to continue or discontinue its use. We believe that there may be some evidence that aspirin would be beneficial during surgery, but as indicated before, the guidelines clearly say there's not enough data. We cannot make any firm recommendation.

And the articles that were included in the medical review from FDA was our initial literature review in March that we discussed with the agency. Subsequently we have done a lot more work, including work by Dr. Avorn, and of course, have looked at more literature and other studies. The Nelipovitz article was just one example of where you could see that perhaps there would be a

beneficial effect of aspirin.

Does that answer your question?

DR. FLEMING: Only partially. Basically what you're saying is now that you've gone further, there are a lot of other sources of information, if I'm interpreting you correctly, that you believe to be more informative and relevant than that article?

DR. BELDER: We believe that with respect to the use of aspirin in surgery there is no firm evidence about continuing or not continuing. There's no well-controlled data.

Dr. Chaitman, would you want to comment on that?

DR. FLEMING: While he's preparing to comment, maybe he can also comment on this aspect as well. Is it fair to say any evidence that we do have comes from observational experience as opposed to any specific intentional randomization?

DR. CHAITMAN: Yes, you're correct. There are no randomized clinical trials looking at aspirin usage in this situation, so it is mainly observational data. That's the reason that there wasn't a discussion of this in the guidelines because the guidelines are evidence-based, and the evidence wasn't strong enough to include them in the guidelines.

DR. BORER: Beverly, you're the committee reviewer. Do you have any issues that you want to raise at this point, or do you want to wait?

DR. LORELL: I'll wait.

DR. BORER: Dr. Fiedorek.

DR. FIEDOREK: Thank you, Rene.

Good afternoon, committee members, ladies and gentlemen. If you'll recall, I was here in an introductory role in January, and I'm now concluding to provide a final framing of the issues and book-ending, we hope, of what we've discussed today and back in January. My purpose, besides giving a brief recap on the issues, is also to provide a final concluding rationale that is based in part on existing FDA regulations that provide the context for what we're considering today.

This list includes the six key components that we described in January and we've discussed to a certain extent today. The first four components, as indicated in the preamble today to the questions that you're considering, were generally reviewed in more detail in January and there was general agreement by the committee at that time and we have not dwelt on these in any additional detail today.

The final two points, highlighted in green, are what we've discussed today, as well as in January. Clearly

in the refiled application, we will now be offering three doses of pravastatin, in addition to the 40 milligrams, the 80 milligram and 20 milligram dose, to go along with the approved doses of aspirin in secondary prevention, 81 milligram and 325 milligram.

The last point has been one that had particular concerns in January, and what we've done today is to review the relevant data. As we've just heard, it's relatively sparse data, but we've reviewed it and I think provided to you the context of using aspirin, or pravastatin for that regard, inappropriately and possibly either continuing or discontinuing either component of this combination in such settings. We've put particular emphasis on the setting of surgery where we've gone into the best data on this particular topic, and we have experts here today to answer those questions as well, should you have further questions.

Overall, with the prescription use of aspirin we are offering in this combination product, we think that the lower doses of aspirin relative to available doses in the OTC setting, as well as clear labeling that this product contains aspirin, and sort of the inherent specificity of prescription use so that the physician is able to implement the use appropriately for secondary prevention in CHD patients, will be meaningful in your considerations.

Overall, we feel that this particular prescription combination product will not impact in any adverse way, in any deleterious way the potential for bleeding during surgery that exists with the OTC availability of aspirin currently.

Besides these six points, I want to now provide a context based on the current FDA regulation for fixed-dose combination products. This particular regulation was actually established quite some time ago in 1971. I think it's worthwhile to read it.

"Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

But I think the emphasis that we provided here in the underlining serves to stress what we've been bringing forward to committee in January and again today, the key components of the pravastatin-aspirin combination. In this context, this regulation from 1971 still provides a valid framework for considering pravastatin and aspirin. The four key components listed here have been met in our view based on discussions in January and again today.

Number one, efficacy through differing mechanisms of action has been met in the setting of secondary prevention of clinical events.

Number two, safety in CHD patients for secondary prevention, including in situations surrounding surgery, is assured in terms of the benefit-risk assessment that we feel exists for aspirin in these settings.

Number three, the key component of contribution which was discussed in most detail in January and that the combination with A plus B being greater than either pravastatin alone or aspirin alone is also a key feature which was determined by the meta-analysis discussed primarily in January.

Finally, we've established that there is a clear medical need in the setting of secondary prevention in a demonstrated population at risk.

Besides these four key features, I think there are some reassuring aspects to the pravastatin-aspirin product as well. As indicated earlier, it's comprised of component drugs at selected doses previously approved by the FDA. In addition, it will be labeled for secondary prevention, an indication previously approved for these component medicines. And finally, practice patterns and medical guidelines support the concurrent use of pravastatin and aspirin as a secondary preventative in the

CHD population.

I think it's quite instructive to consider this last point very briefly here. Generally medical guidelines rely on sort of assessment of benefit and risk as determined by a consensus committee. Recently some of these guidelines have actually outlined risk based on a possible recurrent event over the subsequent 10 years.

In this slide here, the risk of a CHD event in some of the populations represented by the secondary prevention population we intend to treat with the combination are described. These are based on landmark statin trials as well as other sources of information. Shown in the column with the percentages are the placebo event rates in these trials over time. You can see in patients with a history of an acute MI, the risk of a subsequent CHD event, either MI or a CHD death, ranges from 26 percent up to 51 percent over the subsequent 10 years. For patients who've undergone a revascularization procedure, this risk is between 26 and 30 percent, and for patients with stable angina pectoris, this risk is about 20 percent.

I think given these event rates and risks in the secondary prevention CHD population, it's also interesting to consider that recent recommendations and guidelines -- one of them actually mentioned this week from

the American Heart Association recommends the use of aspirin, the one component that we've been most concerned about, in patients who have a relative risk of a subsequent CHD event of 10 percent. Earlier this year, the U.S. Preventative Task Force also recommended the use of aspirin in the preventative setting in patients who had a risk of a subsequent event of 6 percent or greater.

So, to conclude our presentation today, we feel that pravastatin-aspirin is a rational combination that's supported through evidence-based medicine. We are offering three doses of pravastatin to go along with the prior doses of aspirin, 81 and 325 milligrams. The safety of aspirin has been discussed in some detail this afternoon, and we think that the benefit-risk profile in this patient population, the coronary heart disease population seeking secondary prevention, is certainly warranted.

We also have described some possible advantages of using the combination product, pravastatin and aspirin, as a prescription medicine where clear use as a secondary prevention medicine can be designated by the physician and that both physician and patient will know with our labeling that the product, in fact, does contain aspirin.

Thank you for your attention. If there are any other questions, you can call on me and we can also call on the experts assembled today.

DR. BORER: Thank you very much, Fred.

Beverly, why don't you start and then we'll move around the committee if there are any other questions.

DR. LORELL: I think your presentation has been very cogent in addressing the concerns that were raised by the committee at the last meeting.

I'd like to open the discussion with one of several points that I think the committee is going to want to address and that is the issue of recognition of what a combination product includes. I appreciate the query by Steve and your clarification that what we're really discussing here is not the temporary co-packaging of two pills, but the ultimate presentation of both drugs in a single tablet or single capsule. Is that correct?

DR. FIEDOREK: Yes, that's correct. In January, the preface provided to the questions specified that it was a combination co-tablet. As part of our development work for this combination, we will have available both a co-package with each component available to punch out separately, and that will be available initially. Subsequently we will have a true combination tablet, but as Dr. Belder mentioned, it's undergoing stability testing currently.

DR. LORELL: I think one of the themes that many of the questions derive from is the issue of

recognition, not short term but long term, by both patient and clinician provider that a single tablet does contain aspirin, a potent antiplatelet agent. One of the concerns that I would raise, based on my own clinical practice from one of the precedents that we have -- and that is co-packaging in a single tablet or capsule of antihypertensive agents -- is that even though those are often clearly identified on the pill bottle and on the packaging and the labeling, it is extremely common to have confusion not only on the part of the patient as to what a pill actually really contains -- patients know that it is vaguely for their blood pressure or for their heart -- but even on the part of providers.

I guess that one of the pieces of evidence that we don't have, because this is such an important issue, is actually any prospective data regarding recognition of the components. I would welcome comments from others around the table.

DR. BORER: Fred.

DR. FIEDOREK: Yes. We actually took those concerns seriously, and I think the description of how we would describe in the patient leaflet, as well as the clear labeling, as effectively as we can that the product contains aspirin and that both prescribers, physicians, as well as patients, should recognize that.

We have not done anything other than that at this time, and I'm not aware of any label comprehension studies or other label interpretation studies by patients that would address that point from other products.

But I think our main contention is that the prescription use here in this product, as well as the clear labeling that we intend to provide, would not be deleterious at all compared to the current situation that Dr. Belder reviewed with the availability of many OTC aspirin products that may not be recognized by the patient or physician as well. That's a general issue that perhaps the agency would want to address regarding aspirin use in general, and what we're trying to do with pravastatin-aspirin is to be clear that this product contains aspirin and to make it a prescription product for secondary prevention.

I don't know if that helps.

DR. BORER: Steve.

DR. NISSEN: I just want to understand this better. I really like the label that you show here in the slide set. But isn't what happens in reality that a pharmacist has a stock bottle of a product and then they take and they put X number of pills in a container and pass it on to the patient? I mean, these labels aren't likely to appear, are they, on the final product that the patient

is going to actually see.

DR. FIEDOREK: Well, the patient package insert would be part of that product.

DR. NISSEN: Yes. But I mean, this label, which is really terrific, says aspirin three times on it. The patient doesn't see that label.

DR. FIEDOREK: It's currently a proposed label, and perhaps Dr. Temple would want to --

DR. TEMPLE: Well, a point we've made often in the past goes to the very question Dr. Nissen raised. If it's not a unit-of-use package, there's very little reason to believe that the patient will actually get the patient package insert. Now, for the combination, obviously with all the punching out, they will. Sorry. For the co-packaging, then I guess they will because that's how it's going to be given out.

But what about for the combination tablet? Are you thinking of unit-of-use packaging which would assure that the patient labeling goes to the patient?

DR. FIEDOREK: Yes, it would have the same type of intended labeling.

DR. TEMPLE: Well, I know but unit of use or something that the pharmacist has to take an active role in handing out? That's a crucial distinction.

DR. FIEDOREK: Yes, that's our intent.

DR. BELDER: We have not developed the packaging of the single combination tablet yet, but of course, we are listening to you and will definitely take your comments in consideration when we develop that to assure that the patients, indeed, will get a similar type of package as indicated here for the initial co-package with a single tablet.

DR. THROCKMORTON: Steve, you and Beverly are saying that the notion would be that that would increase the awareness of aspirin use. Is that the particular issue you're raising?

DR. NISSEN: Yes. Well, I guess Bev and others of us the last time around wanted to make certain. Obviously, when a combination product is administered, there's a tendency for physicians and patients to lose track of the fact that there's more than one component. So, part of the safety issues related here are to maintain that awareness.

I understand how having a blister pack with that on it, nobody in their right mind could miss it. You put it on there three times. It's very prominent and I think quite desirable.

The problem is a little pill bottle -- I'm not so sure that this label is going to appear. It's very challenging. None of the medicines that I take have