that these symptoms --

I was involved in studies looking at intestinal distress, and people were talking about putting tubes down your throat so that they could measure gas volumes and so forth, as opposed to just asking the person, did you have relief. And that fortunately has gone by the wayside.

I think the question that -- and just to comment, this generalizability is the thing that I think is the real key in terms of how can you generalize from these small studies.

And I hope that they put the word "supportive" of the effectiveness intentionally in the way they wrote this question as opposed to does it resolve the effectiveness. I mean, I'm thinking of supportive as when I look at reviewing NDA and so forth, or reviewing studies -- you've got studies which are pivotal that convince you. Then you have supportive evidence.

I'm taking this supportive to mean that we haven't resolved the question of efficacy with these small studies. But some do show something --

DR. TINETTI: Is that a reasonable -- Susan, is that how --

DR. D'AGOSTINO: -- is that true?

DR. TINETTI: -- you would interpret that as well? So -- that's a good point.

DR. JOHNSON: Two points. The first being we are going to ask you more specifically what the take-home message is in the next question. And the other comment is about the generalizability.

I think there is a reason to reintroduce into this discussion something that we talked about earlier, which is that the advisory panel already made a decision about 10 milligrams. And they used this data, and did generalize, based on that data -- their own clinical experience with the

product at the time, and a large database of marketing history. So there was something that they felt established the generalizability background for them.

We are not asking this committee to try to reinvent that decision, because as you say, I think that is something that's too difficult to do. The question is, in relation to what the petitioner has said, which is that he finds that there is lack of sufficient evidence, do you agree with that is really the question that's on the table today, not to try to revisit what the panel then --

DR. TINETTI: Well, the lack of sufficient evidence is quite different than supportive of. That's a very different --

DR. JOHNSON: Yeah. Well --

DR. TINETTI: But I think maybe we will get to that question too.

DR. JOHNSON: Yeah.

DR. TINETTI: Dr. FitzGerald.

DR. FITZGERALD: So I'd just make the point about the -- the Parker points, and that is relief of symptoms, and I concur entirely. But before we completely jettison attempts to have objective measurements of reality, I'd remind you of the data that were shown to show the multiple administration of dose and the response waning over the dosing interval. And exactly the same thing happened in the placebo group. So you have not just a dosing effect of placebo, you have a dosing effect that wanes over the same dosing interval with placebo.

So you're trying to detect a true effect that as measured by patient symptom relief is quite simulated by placebo response. And just to add to the arguments that have been made from a statistical standpoint as to how the odds are weighed against being able to detect efficacy, or indeed, dose response, from a pharmacological point of view, that's true too. It's true

both from the point of view of the nature of the placebo response of the variability of drug response relative to sample size, and also the dynamic range of the endpoint measurements that are being talked about.

So I think the ground is not neutral in terms of the predictability of being able to detect a response a priori from a pharmacological point of view, even if we had no data.

DR. TINETTI: So Susan, is that sufficient discussion for you? Okay, great. Thank you. Let's move on to the second question, and we'll be doing voting. And for those of you who weren't here yesterday, you have your little pads here. And what we'll do is -- and Susan has said that she actually does want us to specifically do "yes" or "no" for each of the four points of question too. And she assures us she understands they are not necessarily exhaustive or mutually exclusive. But these are the specific

questions she would like us to address.

So how we will do this is, "1" is "Yes," "2" is "No," and "3" is "Abstain." Everyone will vote simultaneously. And I think what we have been asked to do -- it takes about 20 seconds to tabulate -- is that correct? And once it's been tabulated, then we will have all the "yeses" raise their hand. And we'll go around and say their names so it goes into the records, and then we'll have all the "noes," and then the "abstain." Any questions on the voting?

Okay. So the question we are asked to vote on is, the following four statements represent alternative summary assessments of the data presented for phenylephrine. Please consider each statement and vote yes or no on whether it represents your conclusions about the data. So the first question is, "Phenylephrine in a 10-milligram immediate release formulation is effective when dosed every 4 hours for the symptomatic treatment

of nasal congestion, and no additional studies are needed."

So "1" is "Yes," "2" is "No," "3" is "Abstain."

DR. FITZGERALD: Question?

DR. TINETTI: Pardon? No, no, no. This is supposed to be that the data are sufficient and no further -- Susan -- pardon?

DR. FITZGERALD: They are two separate issues --

DR. TINETTI: Well, I'm not sure. I think -- are you understanding the spirit of this question? The data -- we are asking specifically that the evidence to date shows that it is effective and that you do not feel that further study is needed. So this is one question.

DR. SHRANK: Needed for what? What is needed?

DR. TINETTI: Is needed to show its effectiveness.

DR. D'AGOSTINO: And we are talking

-- we are not talking that we are trying to strike out what was done before, but what we think a study should look like, and what we think is the (off mike) in order to show effectiveness. Is that right?

DR. TINETTI: Correct. Is that an accurate assessment? So to clarify again, is -- Garret is confused that -- he thinks those are two separate questions. So can you clarify why you think that is a single question?

DR. JOHNSON: I would --

DR. FITZGERALD: I think -- oh, sorry.

DR. JOHNSON: I would use these as characterizations of your summary of the data rather than two separate questions. Is this how you characterize the data, yes or no.

DR. FITZGERALD: Well, then I'd have two separate answers to what you --

DR. TINETTI: So you are saying that it's --

(Laughter)

DR. JOHNSON: If you look at some of the other options, you may find the one that you are concerned about.

DR. TINETTI: Yes. That's what I'm saying. These questions are not sort of mutually exclusive. I think the way to interpret this is that you think the data are conclusive. So you would answer yes to number 1 if you think the data are conclusive of effectiveness.

DR. NELSON: Can I make a comment on that? Nelson. I mean, I've never been to an academic seminar where anybody though there was a -- the answer was -- I mean, I think it's a foregone conclusion that everybody and every academic in the world wants another study. And I mean, if I -- with all due respect, to me it's sort of a pre-determined question. If it could be separated, it might be a little easier.

DR. JOHNSON: It's fine if the

answer is no. And if everyone chooses to vote no, that is a very realistic response. We are okay with that. The other questions we'll get to if you want additional studies about what do you want the additional studies.

DR. FITZGERALD: Could I suggest that we just omit the last sentence and answer the question?

MR. GANLEY: I'm Charlie Ganley; I'm director of the Office of Nonprescription Products. The way these questions were formulated was to try to help us sort of understand part of the discussion here. Certainly someone here could think there's some effectiveness data, but we'd like more data, okay. And we understand that. But I think if you go through the progression of questions, you know, we'll arrive at that. B and C sort of say that we think it's effective -- I don't have it in front of me. Yeah, B and C really say it's effective, but

we want some more data, okay. We think there's some effectiveness data.

It's really -- we have to make some regulatory decisions here as we go forward, and the monograph is very different than, you know, looking at individual NDAs. But you could answer these questions and say that I think there is -- you know, there's some effectiveness data, but I want more data. So the answer to this would be no.

(Laughter)

MR. GANLEY: I had to read it again. No, but if you want, you know, we're trying to draw out the discussion here. It's easier for us to understand what the committee feels.

If they think there's effectiveness data, that will be captured in B and C. And if there's a need for additional studies, that will be captured in B and C. So in this question, you have to feel that we think there's -- you could say that there's

effectiveness data. We don't think there's any more data that's needed, and we are fine with that. So if that's the way you feel, then you answer as is. And I think -- but again, it's really to try to extract what does the committee want out of this. And I think we've heard a lot of discussion already, and we've got a sense of, you know, where you are heading.

But that was our intent, because we do have to make some regulatory decisions here of how to move forward. You may find that there is some effectiveness data, but we still want some more, you know, some additional data with regards to safety and blood pressure and things like that. So --

DR. D'AGOSTINO: I cheated and looked ahead --

(Laughter)

DR. D'AGOSTINO: The concerns I have aren't necessarily captured in B and C. I mean, I want -- my concerns are -- I'd like

to know that this does in fact work across the population that, you know, the target population is being addressed. I'd like to say something about the dosing interval, but I'm more interested in the sort of generalizability, getting big studies that really show effectiveness. And are they supposedly captured in B and C? I don't see them. I mean, when the B talks about dosing interval and C talks about 25, I don't really care about 25. I mean, it would be nice to do that, but that's where the academic comes out. What I really want to know, is 10 effective for a broad population.

DR. TINETTI: Can I make a suggestion that we really consider A as -- that the data are sufficient to conclude that it's effective, yes or no. And then as, Ralph, as we move on, I think what we will do is, say, if additional studies are needed, then we will volunteer what we think those additional studies should be. Is that --

DR. D'AGOSTINO: Can I say -- I thought the FDA was giving us little hand calculators. I was so excited.

(Laughter)

DR. TINETTI: You cannot take it with you. So let me word it as I think we have decided.

Phenylephrine in a 10-milligram immediate release formulation has been shown to be effective when dosed every 4 hours for symptomatic treatment of nasal congestion, and no additional studies are needed to support its effectiveness. Okay.

SPEAKER: We did that one, right?

DR. TINETTI: No, that's the one we are voting right now.

So that is "Yes," "No," or "Abstain." So we are re-voting.

I think some people have voted. It's not coming up. Try pushing it harder.

(Laughter)

DR. TINETTI: So you're wanting us

to wait until it tallies before we do the hand vote?

SPEAKER: (Off mike)

DR. TINETTI: No hand -- Okay. So now we have to do the hand vote. I don't know why we have to do both, but anyway. So those who said yes raise your hand, and just read it -- do your name.

DR. HONSINGER: Richard Honsinger.

DR. TAYLOR: Robert Taylor.

DR. TINETTI: Noes, raise your hand.

DR. SHRANK: Will Shrank.

MS. PARKER: Ruth Parker.

MR. OWNBY:: Dennis Ownby.

DR. LEVIN: Arthur Levin.

DR. TINETTI: Mary Tinetti.

MS. HOFFMAN: Ruth Hoffman.

DR. GRIFFIN: Marie Griffin.

DR. FITZGERALD: Garret FitzGerald.

DR. FOLLMANN: Dean Follmann.

DR. D'AGOSTINO: Ralph D'Agostino.

DR. NGO: That's a total of 2 yes, 10 noes, 0 abstentions for a total of 12 votes.

DR. TINETTI: All right. We enjoyed that. Now, let's see if we can --

(Laughter)

DR. TINETTI: -- the wording for B. As it presently reads, it's "Phenylephrine in a 10-milligram immediate release formulation is effective. Additional study is needed to identify an appropriate dosing interval for this dose" -- "appropriate interval for this dose." So again, to interpret this question that there are suggestive data of effectiveness, we agreed that it's not definitive. And the only thing you want to know at this point is whether or not we think these additional studies are needed purely to address interval.

Okay. So to answer this question, yes, you'd have to say, yes, you think that the evidence supports effectiveness, but no,

we don't know enough about interval. Is that correct, Susan?

DR. JOHNSON: Yes.

DR. TINETTI: Okay. Does everybody understand that question, or --

MR. OWNBY:: I've -- this is Ownby. I've got a question of whether these are supposedly mutually exclusive or not?

DR. TINETTI: No, I said at the beginning, they are not exhaustive nor mutually exclusive.

DR. SHRANK: So if one were to say no to this, you could be saying no to either part.

DR. TINETTI: Right. Yeah, this one I think is more problematic than the first one. Because if you -- so we -- right. If you don't think that -- you almost have to say whether or not we think that there is sufficient -- that the evidence is only suggestive of effectiveness. I think we -- this is when we have to break up into two

parts. This one I don't think we can combine into a single question.

MR. GANLEY: It's Charlie Ganley again. Yeah, why don't we just do that and the -- I think what we are trying to arrive at, if people may think it's effective, but they still want more additional studies done. Okay. And this one --

DR. TINETTI: So it seemed to me first --

MR. GANLEY: Why don't we just do if people are more comfortable to get rid of the second part here and see if people believed it is an effective dose? And then we can address the latter question here and see, okay?

DR. TINETTI: Okay. So the only question we are addressing here is -- again, the discussion has shown that I think nobody believes that the data are overwhelming for effectiveness. The question is that --

MR. GANLEY: Let me -- let me --

right, let me just --

DR. TINETTI: -- that -- is that suggestive of effectiveness.

MR. GANLEY: Right. Let me just let people understand the process, okay. For us to say to change the monograph, we would have to say that we have some concerns about the data we have. And we are going to have to make some changes to the monograph. And so we would have to go through the regulatory process. Now, the way question A on this was written is that you are fine with all the data. I don't need any more data. I think it may be effective, but I don't need any more data. If everyone answered yes on that, we'd be pretty much done because it would tell us that we don't have to do anything with the monograph.

So what these questions were trying to arrive at is -- you know, I think it gets to the -- a lot of the issues that have been brought up with regard to, has an adequate

population been studied, do we have sufficient evidence or information on blood pressure and things like that. We still may think it's an effective dose, but we may still want more information.

If it makes people feel better on B, just answer, do we think it's an effective dose without any connections. And then we can go on to C, and if you think it's an effective dose, you take, well, what studies do you think you want.

DR. TINETTI: Okay. So how I would word this is that there are data supportive of effectiveness of this 10-milligram dose of phenylephrine.

MR. GANLEY: Yes.

DR. TINETTI: Not a definitive, okay.

MR. GANLEY: That's right.

DR. TINETTI: Does everybody agree to that -- understand that question?

DR. LEVIN: Well, that's not how I

interpret "is". "Is" is a -- "is" to me is a very positive statement. I mean, I think there is a distinction between supportive and --

DR. TINETTI: There is. That's why I'm making sure that we are all answering the same question. So we are not being asked to definitively state whether we feel the existing data unequivocally support its effectiveness. Is that correct? We are asked, given the data that exists, is there evidence supporting a possibility or probability of effectiveness. So that's a -- it is an important distinction.

DR. FITZGERALD: How about for clarity just saying, actually rewording it, and saying the formulation appears to be effective, additional studies are needed? Because that gets away from the focus on the dosing interval -- I mean, there may be other things you want to get at.

DR. TINETTI: But we are ignoring

the dosing interval completely for this one.

DR. FITZGERALD: Yeah. If you say, "Appears to be effective," it captures that flavor. And then you just couple that with "additional studies are needed."

DR. HONSINGER: Can't you just cross out the first sentence and just say we are voting on whether additional study is needed to identify an appropriate dosing interval?

SPEAKER: Yeah.

DR. TINETTI: No, because -- we can't do that, because we've never really clarified whether people think it's effective. And if you don't think it's effective, then the dosing intervals are --

SPEAKER: -- dosing?

DR. TINETTI: No, no, that -- well, not according to that vote.

DR. D'AGOSTINO: Can we put this -- if we take the sentence that the 10-millimeter immediate release formulation

is supportive of effectiveness, isn't that what you said? I mean --

DR. TINETTI: That is what I said.

DR. D'AGOSTINO: So can't we just write it that way, and that's what we are voting on?

DR. TINETTI: That's what I would suggest. But I think everybody was not in agreement to that. I think that's still what -- in the spirit of what -- I think that's what's most in the spirit of what FDA is asking us.

DR. D'AGOSTINO: Asking us, yeah.

MR. OWNBY:: And we are talking about clinical effectiveness here --

(Laughter)

MR. OWNBY:: -- as opposed to a physiologic measurement.

DR. TINETTI: I think this is where you are going to be voting based on your own expertise and interpretation of the data, when we get to the additional studies that we

think are needed. And so if you feel that it requires symptomatic benefit to have even suggestive effectiveness, that's how you should vote. If you feel that physiologic is sufficient, then that's how you should vote. Is that correct? That it --

DR. JOHNSON: I think that we have an internal discussion all the time, in every NDA that we look at, in every efficacy decision we ever look at, about specifically that question. And we might want to discuss it later, but vote with what you think is the right way to approach how we would label this product. Do you have sufficient evidence to put the indication -- continue to put the indication that's on the product, on it?

DR. TINETTI: All right. We have to reword the question. And I think where we had, given the available data that exist, the evidence is suggestive that the 10- milligram immediate release formulation is effective.

DR. NELSON: Is the word suggestive

or supportive?

SPEAKER: Suggestive.

DR. TINETTI: What's that?

DR. D'AGOSTINO: Why don't we use supportive? That's what we tend to use.

DR. TINETTI: Supportive, I'm sorry, supportive. Okay. Everybody understand the question? Okay, so again, "1" is "Yes," "2" is "No," and "3" is "Abstain." Okay. Can we have all the "yeses" raise your hand? Okay, go around.

DR. SHRANK: Will Shrank.

MS. PARKER: Ruth Parker.

DR. TAYLOR: Robert Taylor.

DR. HONSINGER: Richard Honsinger.

MR. OWNBY:: Dennis Ownby.

DR. LEVIN: Arthur Levin.

DR. TINETTI: Mary Tinetti.

DR. FITZGERALD: Garret FitzGerald.

DR. FOLLMANN: Dean Follmann.

DR. D'AGOSTINO: Ralph D'Agostino.

DR. TINETTI: Noes?

MS. HOFFMAN: Ruth Hoffman. There was two of us.

SPEAKER: Got a ringer.

DR. TINETTI: Who's not fessing up?

SPEAKER: Dean voted twice.

(Laughter)

DR. FOLLMANN: I didn't vote -- I would have voted yes, but I didn't have a button. So it is not me.

DR. TINETTI: Okay, how many -- do we have to re- vote?

DR. JOHNSON: Yeah, I'm not sure that I really interpreted the question correctly with supportive either.

SPEAKER: Michael Levin.

SPEAKER: What?

SPEAKER: No, I had, yes.

SPEAKER: Okay.

SPEAKER: Don't ask me to remember what button I pressed.

(Laughter)

SPEAKER: I intended "yes."

SPEAKER: Change his vote to a yes.

SPEAKER: I can't reconstruct --

DR. TINETTI: Hopefully there's no hanging chads.

DR. NGO: Okay. That is a total of 11 yes, 1 no, 0 abstentions for a total of 12 votes.

DR. TINETTI: All right, it gets even murkier.

DR. JOHNSON: Maybe I can clarify the intent of this --

DR. TINETTI: Thank you.

DR. JOHNSON: -- before you get started. Given that we've said that there are data that are supportive of the 10 milligrams, this question is really to say in addition to that, do you want to see studies of the higher doses. In other words, do you think that the 10 should stand alone as the only dose, or should we start to encourage industry and think about what would happen with the higher doses, in addition to the 10?

SPEAKER: I think you can also broaden it to say if people have other studies, because there's obviously other studies that people --

DR. JOHNSON: Let's do that at the end. Let's just stick to the dose for the moment, because they are kind of --

DR. FOLLMANN: Actually I'd still like to see studies of the 10. To me the data are suggestive, or if I had to bet, I would bet. But I don't think the question is settled to my -- you know, definitively, from my point of view.

DR. TINETTI: I think -- what I'm -- I'm almost wondering if this would be more effective if we just went around and people sort of said what additional studies -- we've already agreed that we need additional studies. So rather than --

DR. JOHNSON: Could we vote specifically on the dose question, that you would like to see studies of higher doses,

given the answer to the last one, and then talk about what other studies, generalizability, larger studies, that sort of thing?

DR. TINETTI: And you feel that that's an important FDA question, fine, okay.

DR. JOHNSON: Because that's a petitioner question as well.

DR. TINETTI: Okay, fine.

DR. JOHNSON: Thanks.

DR. TINETTI: Reasonable. Okay. So the question would be then -- I think we'll just start with question -- the second sentence. Additional studies are needed to assess the efficacy of a higher dose, such as 25 milligrams. Forget the dosing intervals. Let's keep it straight. Is that -- okay, is that fine? Does everybody understand the question?

DR. FITZGERALD: Glad to say I'm the last boy in the class.

DR. TINETTI: You are not -- you're

not the only one.

DR. FITZGERALD: Efficacy and safety presumably. I mean, all pharmacologists love to see dose-response relationship, even if what you are trying to do at the end of the day is understand what's happening at 10 milligrams. But --

DR. TINETTI: So efficacy --

DR. FITZGERALD: Efficacy and safety.

DR. TINETTI: Efficacy and safety.

DR. FITZGERALD: Yeah.

DR. TINETTI: Fair enough. Yeah, did you have a comment on the question?

DR. D'AGOSTINO: No, it's exactly the same.

DR. TINETTI: Okay. So the wording of the question is then, additional studies are needed to assess the efficacy and safety of higher doses, EG 25 milligrams.

SPEAKER: (Off mike)

DR. TINETTI: I know, we just said

it. He's adding it now.

Okay. Everybody understands the question. Efficacy and safety.

DR. FITZGERALD: Yes, safety hasn't made it in there yet.

DR. TINETTI: Marie.

DR. GRIFFIN: I'm still sort of perplexed about why they are needed. I mean, they are needed because the petitioner asked for it. But we don't -- I'm not sure why we need --

DR. TINETTI: Is there a reason other than that's what the petitioner asked, since we have to address what the petitioner asked?

DR. JOHNSON: The intent of the question was to understand whether or not the committee felt strongly about having an additional dose, if they felt that the 10 was effective. So I think you've confirmed that there is supportive evidence of efficacy of the 10. Now, do you feel strongly that it

may be at the lower end of the dosing range, and we really should have data on higher dose?

DR. TINETTI: So is it fair to say, if you are convinced that the 10 milligram is safe and effective, and that should be what's available, you would vote no to this question. If the data may be supportive of the 10 milligrams, but you are not sure, and that perhaps you think a higher dose may remain safe, but be more effective, you would vote yes.

DR. JOHNSON: I think you could even answer the question independent of what you think of the 10. It could be a generalizability question. The 10 doesn't look like it's generalizable to everyone, even though it does have some supportive --

DR. TINETTI: Fair enough. So it could be more choices. Okay.

DR. JOHNSON: Right.

DR. TINETTI: Fair enough. Does

that explain for you -- now, that's a good -- okay.

DR. NELSON: Can I -- could I just make one comment? Because this is almost a demand type of answer, it would be better to say, "may be needed," because of the way it's questioned now, it almost demands another study.

DR. JOHNSON: I think given the current level of data, "may be needed" is sort of obvious in that we know that there is less data than we might like about any dose. So "may be needed" is a little less strong than what we were actually looking for. We have a limited ability with monograph products to require industry to look at additional -- to do additional studies, to look at additional parameters, whatever they may be. And this is -- we are really looking for feedback from the committee about what they think the marketplace should be informed by.

DR. TINETTI: Okay. All right.

MS. PARKER: Just one question. Currently they are eligible to create the product and make it available up to 25 or up to 60 or up to 200 or --

DR. JOHNSON: We looked at this question hypothetically. At this point we know that the advisory panel looked at 25, and therefore, 25 is eligible to be considered under the monograph. We don't really know, based on the records, that any higher dose would be eligible under the monograph, but could be submitted under an NDA. And that's not -- for the sake of industry here, that's not a definitive response, that's our initial hypothetical look, that the 25, were we to get data, could be eligible for marketing under the monograph, could be evaluated under the monograph. Anything higher than that would most likely have to be evaluated under an NDA.

And that's based on what was marketed at the time the panels looked at the initial universe of products. It's all how the monograph is set up.

MS. PARKER: Is there a way to say 25 is a single product for evaluation and sale?

DR. JOHNSON: You mean as a single ingredient? I think we've captured that comment. And I think that that's something that's going to be reflected in the comments that --

DR. TINETTI: Yeah. I think we'll get that later when we talk about what kinds of studies -- okay.

DR. JOHNSON: Yeah.

DR. TINETTI: All right. Let's go to a vote then. The question is, "Additional studies are needed to assess the efficacy and safety of a higher dose, such as 25 milligrams." Yes, no or -- all right, "yeses" raise your hand. We'll start on this

side this time.

DR. D'AGOSTINO: Ralph D'Agostino.

DR. FOLLMANN: Dean Follmann.

DR. FITZGERALD: Garret FitzGerald.

MS. HOFFMAN: Ruth Hoffman.

DR. TINETTI: Mary Tinetti.

DR. LEVIN: Arthur Levin.

MR. OWNBY:: Dennis Ownby.

DR. HONSINGER: Richard Honsinger.

MS. PARKER: Ruth Parker.

DR. TINETTI: Okay. Noes?

DR. SHRANK: Will Shrank.

DR. TAYLOR: Robert Taylor.

DR. GRIFFIN: Marie Griffin.

DR. NGO: That's a total of 9 yes, 3 noes, 0 abstention, for a total of 12 votes.

DR. TINETTI: I think we are scheduled for a break, but we are almost finished. I just think we are just going to go ahead and finish. Now, I do not think we need to go to D. I think we have already --

my understanding is we've -- with our rewordings of the questions, we have addressed D.

DR. JOHNSON: So if I'm understanding the response to B, there is one person who believes that the data do not appear to be supportive of the 10-milligram dose, is that correct? Okay. I just want to make sure that was the -- the "no" answer, that's what that meant.

MS. HOFFMAN: It was, but it was sort of an interpretation of supportive too. So --

DR. JOHNSON: Okay.

MS. HOFFMAN: Yeah, I could probably go either way.

DR. JOHNSON: It might help before -- well, actually, we could either discuss before the next question or just add on to the next question what additional studies would you like to see.

DR. TINETTI: I think it's really

part of the next question. And again, here I don't think we need to vote, right. I think this is just giving you suggestions of the types of studies.

DR. JOHNSON: I think the only thing that might be helpful to vote on is whether there need to be additional studies. And if everybody feels like that's already been covered in 2C then we are fine.

People did vote in 2C that we needed additional studies. So --

DR. TINETTI: Right. I think we already voted on that.

DR. FOLLMANN: Wasn't -- I hate to belabor this, but wasn't 2C for 25 milligram?

SPEAKER: Yes.

DR. FOLLMANN: And so if we want to have a study of 10 milligram, that -- which I would --

DR. TINETTI: All right, let's do that. Okay. So the question is, are additional studies of 10-milligram dose

needed? Yes, no, without getting to details of what would be obtained. Okay.

Can you write us a new question? We took out the additional -- we took out the question -- we separated, and we never went back to address that question there, right?

DR. JOHNSON: So I don't think that we need a question on -- another specific voting question. We could just ask the question, what additional studies. And if it's about the 10, that's fine. If it's about the 25, that's fine.

DR. TINETTI: So we don't need to vote?

DR. JOHNSON: I don't think we need to vote at this point.

DR. TINETTI: Fine. Okay, so now we can just open it to discussion of the types of studies that we think are needed. Okay?

DR. JOHNSON: Right. And the only thing that I would do is just ask you to

include the concept from the third question about potentially we don't have the right dosage form at this point, that an extended release dosage form, such as Schering suggested, might be the right way to dose this, just include that in the discussion.

DR. TINETTI: Right, that could be part of that. Okay. And I know people have made suggestions along the way, and I think, please reiterate those now because I think this -- we'll be tabulating that.

Ralph.

DR. D'AGOSTINO: Ralph D'Agostino. I think that -- at the 10 dose, I think we need to have better understanding of generalizability. So I think we need multi-center studies with age, gender, race, and severity, the plethora and the spectrum of those variables covered. I think the outcome measures should be on the symptoms, the nasal congestion score or similar things.

Objective measures may be

secondary, but I think the symptoms should be primary. I think the study should be parallel sample studies and not crossovers. They should be placebo -- randomized placebo, double blind. And I -- this is my wish list, and I think it should be done. And I think they should have positive controls in the studies. And this should be studies for common colds, and also for rhinitis.

If you have the 25 -- I'm not so sure that studies have to be done with 10 and 25 simultaneously. But I think there should also be studies that do have 10 and 25, some studies that are looking at the dose response in terms of efficacy and also safety. And I think the questions like the blood pressure -- effect on blood pressure should be pinned down, and studies should be designed for those.

DR. TINETTI: So I assume nobody's going to disagree with Ralph on those points, so any additional studies.

MS. PARKER: I'm concerned that it's easier and clear for us to talk about a single ingredient, and effectiveness and safety about a single ingredient, but it does not reflect the reality of the marketplace and what the person with the common cold faces. And I think we really need to focus in on that in order to -- I mean, what we are talking about is a stuffy nose with a bad cold. And it becomes very crystal clear when it's one -- well, not that clear. But it becomes clear when it's one ingredient in one dose, but the marketplace doesn't reflect that. The marketplace is reflecting to the person with the common cold a panacea of products, very few of which have the single ingredient in it. And so --

DR. TINETTI: So are you suggesting that -- I'm not sure, are you suggesting that they need both single- ingredient and multi-ingredient studies?

MS. PARKER: I think the ideal

thing is that the marketplace should have single-ingredient products available for the consumer about which we understand safety and effectiveness. That is not the question on the table.

DR. TINETTI: But that's not the situation. Given the situation, what are you suggesting we need?

MS. PARKER: Well, given the situation, I think this is another reason to point out how much that's needed to the FDA, which we have said in the past.

MR. OWNBY:: I would suggest if we did have studies that showed good safety and efficacy that at least with combination products that they show that there are not major changes in the absorption and distribution of the drug because of the combination. We see very many drug interactions. And with these combination ingredients if you assume that most of those are truly active ingredients, then I think

that there is an onus to show that they are not affecting dramatically the blood levels achieved.

DR. D'AGOSTINO: We are -- I mean, with the study I was describing, the first study, was just for the single dose. We are not saying they have to be combinations, right, to begin with. I was -- what I said single dose, and now, in addition, there should be combinations.

MS. PARKER: Which gives confidence about the single ingredient, you know, for us making a decision, but for the consumer, that didn't really help --

DR. D'AGOSTINO: I agree, I'm fine. I just want to make sure that I heard you correctly.

MS. PARKER: Yeah. So I think as we ponder it, it's just not about the single ingredient. It's about the reality of what you face when you have a common cold and a stuffy nose.

DR. D'AGOSTINO: There are a lot of different possibilities. There's four different ingredients that they tend to put in these things. And two at a time, three at a time, or four.

DR. HONSINGER: In Dr. D'Agostino's study, I want to add another arm. I want an arm with a drug that we think is effective. I think we should have the racemic ephedrine --

DR. TINETTI: He mentioned that.

DR. D'AGOSTINO: Yeah. I said the --

DR. HONSINGER: Yeah.

DR. D'AGOSTINO: Yeah. I said that.

DR. HONSINGER: And I guess the second thing is I want to make sure we look at adverse events. I think one of -- a couple of the adverse events we don't -- we haven't looked at, and we ought to be looking at, and haven't been mentioned today, when I

see patients as an internist, I frequently have patients, at least several times a year who came in with ectopic cardiac beats due to their pseudoephedrine. And the question is will that happen with phenylephrine as well. If they are getting ectopic beats, we are going to see a few cases of atrial fibrillation, going to get the extra cardiac alpha receptor stimulation. So I think we should look at that.

We should look at the urinary effects when we do a population of more than just medical students back, when medical students were young.

(Laughter)

DR. JOHNSON: I just wanted to ask the committee if they wanted to characterize what their idea of an active control should be. I think there is something unsaid here that maybe pseudoephedrine is a more effective product. Is that the assumption that folks are making?

DR. D'AGOSTINO: That's what I have in the back of my mind. And it's not that it's more effective, I think we have more evidence that it is effective.

MS. HOFFMAN: I'd like to see comorbidity studies as well on type 2 hypertension and see how, you know, other conditions would be impacted. I mean, similar to what you are saying. If you've got, you know, an ageing population or an increasingly obese population with, you know, type 2 diabetes and metabolic syndrome and all these things, you know, what does that do when you take a vasoconstrictor.

DR. FITZGERALD: Yeah, I'd just like to sort of amplify that. I think what we really need are studies that relate dose to plasma concentration to effect, both in terms of efficacy and potential adverse response. And with respect to blood pressure, which, let's face it is the surrogate of an adverse effect we are most

concerned about, besides it being appropriately powered to detect a reasonable effect, which could be clinically quite important, like 3 or 4 millimeters of mercury systolic, and using contemporary approaches to measurement of blood pressure, I agree that this should be performed in a hypertensive population who might amplify the likelihood of detection of signal.

And we should also look at the effect of time of day of dosing which has been shown to modulate the hypertensive response to phenylephrine in humans.

DR. TINETTI: Just before -- a few questions, do people think that we need studies looking at different intervals and extended release, or is that --

DR. HONSINGER: That's my point. From the data that Schering showed us, I mean, we certainly would -- you know, suppository or an enema, this drug would give an overdose.

(Laughter)

DR. HONSINGER: So I think we need to look that this drug is very dependent upon its delivery system, as to where it's absorbed. And that needs to be looked at on any delivery system we use with this drug.

MS. HOFFMAN: I guess one more thing is if you could look at it from a genetic factor, in terms of metabolism -- I don't know if that's doable. But I would think with all the genetic techniques that would be something that would be pretty cool, to see if a certain population or a certain genetic trait metabolizes better than others. I don't know.

DR. TINETTI: Okay. Anything else? Is our work done here today?

DR. JOHNSON: Thank you very much.

DR. TINETTI: Thank you.

(Whereupon, at 3:15 p.m., the PROCEEDINGS were adjourned.)

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