of the equipment, which is pretty technically complicated as you've heard. Well, now, it's even more technically complicated than the one hanging on your tree, but are hopefully not hanging on your tree.

And I would just like to -- I did contact Dr. Eccles prior to this meeting just by e-mail to ask what he thought about that question. And he said that he would prefer NAR if the interest was in a physiological as opposed to a symptomatic change. And I would just quote him, "Decongestant claims should be backed with an objective demonstration of effectiveness, whereas claims of symptom relief should be backed up with or supported by changes in symptom scores."

So our standard in DPAP I believe is symptom relief. In that case then subjective scores would be the -- even he would acknowledge as the preferred way to go. But correlation in general is not very good.

For example, you can take menthol and have someone whose nose is blocked up and give him a whiff of menthol and they feel -- because they get the sensation of moisture in their nose -- they feel decongested even though they're not in terms of measuring obstruction in the nose. Okay.

DR. FITZGERALD: I was impressed with the information provided by Dr. Koenig that didn't appear to even be consistent with dose-response relationship and I wondered if there was any information relating to dose-creep in the field? Do we know how people behave with respect to dosing out in the field or has that ever been studied?

DR. JOHNSON: When you say dose creep, do you -- you're referring to patients who --

DR. FITZGERALD: Keep taking more drug because they don't get a response.

DR. JOHNSON: We were interested when we started this project, in

characterizing the degree to which the oral formulation was included in the monograph, because at that time the nasal product was pretty prevalent. The nasal topical products were generally more widely used and we were unable to really be able to assess what -- how the panel viewed any of the carryover, such as rebound congestion and that sort of thing from the previous dosage forms.

So we couldn't really discern if they ever intended it to be used with the nasal topical formulation, if their practice taught them that there was a different dose to be used. We didn't really get a good characterization except what had really been written down in the rulemaking. There just weren't record. So I think that we have to make the assumption that we are really looking at the 10 milligram as the dose that's used.

And we do have some safety information that shows that when name brand

products were reformulated from pseudoephedrine to phenylephrine, there was confusion and when people actually got what was a higher dose, because they ended up taking two tablets instead of one, there were adverse events reported.

So in terms of the subjective experience of adverse events, nervousness, headaches, that sort of thing, we do notice a dose range, but I think in terms of this -- the efficacy portions of these studies there wasn't a good dose range demonstrated between 10 and 25 and we really don't know how that conveys to what patients use in day-to-day practice.

DR. TINETTI: So in other words, we don't know?

DR. JOHNSON: I don't think we know.

DR. TINETTI: Okay, thank you.

MS. PARKER: Is there any data on rebound?

DR. JOHNSON: We don't have any. We don't know that it occurs. We don't -- we haven't seen that that's a problem. Industry might be able to answer some of that additionally.

DR. TINETTI: Thank you. I think we will take a 15-minute break and convene about 10 minutes after the hour. And panel members, just remember, there should be no discussion during the break among yourselves or with any member of the audience. Thank you.

(Recess)

DR. TINETTI: -- presentation, and before Dr. Hendeles' presentation, I'd like to remind the public observers that this meeting is open for public observation, but public attendees may not participate except at the request of the panel. And also, for the petitioners, I think two of our presentations will be by individuals who are on the phone, who will be taking questions

but their presentations are recorded.

So, Dr. Hendeles, thank you. Did I pronounce that correctly? Your pronunciation of your name?

MR. HENDELES: Hendeles.

DR. TINETTI: Thank you.

MR. HENDELES: I don't think this microphone is -- now, it's on. Well, thank you very much for allowing me to make this presentation and I just admire all the work that Dr. Koenig and his staff did. It was an enormous task and I think only Dr. Hatton would appreciate it, because he did the same thing on our end.

I should mention that according to Dr. Nove that citizen petitioners are not required to disclose any financial conflicts, but I would like to disclose that I'm on the speaker's bureau for Schering- Plough for their asthma drug, and Dr. Shuster's wife has a tiny bit of stock in Pfizer, the manufacturer of Sudafed.

My presentation is going to cover five points. The first is that an oral dose of phenylephrine at 10 milligrams is no more effective than placebo. That at 10 milligrams, there is no clinically relevant systemic effects and the reason for that is it has poor oral bioavailability. What's really needed is dose -- appropriate dose response studies to define what dose of phenylephrine would overcome this poor bioavailability and give adequate clinically important nasal congestion without important side effects. And lastly, I want to point out that the current TV ads for these products are grossly misleading the public.

Back in 1977, Dressler conducted a study examining the effects of different routes of administration of decongestants. There were three products in this study -- actually three cohorts. Each cohort received active drug and placebo in a double-blind randomized crossover design during a 2-day

period when they had nasal stuffiness from a naturally occurring common cold.

One of the products was an aromatic inhaler containing camphor, menthol, and desoxyephedrine which is a levo form of methamphetamine. The second product was 60 -- 50 milligrams of oral phenylpropanolamine, which is no longer on the market because of its association with hemorrhagic stroke, and the third was topical Neo-Synephrine, phenylephrine nasal spray at 0.25 percent.

The congestion index was measured by rhinomanometry and you can see quite clearly that the topical application of this alpha-adrenergic agonist produced profound, nearly 80 percent, decrease in nasal airway resistance, which was significantly greater than the 40 percent from the oral, but the oral course lasted longer than the phenylephrine.

Now, they also measured symptom scores in this double-blind randomized

crossover design and I want to point out two symptom scores -- number 4, which was the mean scores on the 2 consecutive days that they had treatment and placebo for the phenylephrine. And it's defined as nostril feels blocked and it's not comfortable breathing through the nostril, and I want to point out a score of 2, which is what they were reduced to -- almost clear, can breathe through this nostril quite easily. And I think these are very important points, and certainly, I agree that this is much more relevant than nasal airway resistance, which is a pharmacodynamic endpoint.

But the drug has to relieve these symptoms, and I think a clinically relevant amount is going from quite stuffy to almost clear.

And this is the symptom scores, the percent differences between placebo and active drug, or in parentheses, you can see they start off at a score 4, they drop down

to a peak of 1.5, and over a period of 2 hours slowly rise to a score of 2. So they went from significantly blocked to almost clear by symptom score. And I think that's the kind of difference you want to see if you've got a stuffy nose and it's keeping you awake at night.

This is the Bickerman study that was referred to earlier and I present it because it was my first exposure to a study that actually compared, in a randomized crossover design, different decongestants. And they used nasal airway resistance. It was double-blind and randomized, but we didn't include this in our meta- analysis because there was no standard deviations, just the means were presented. But I want to point out that both phenylephrine and -- or excuse me, both phenylpropanolamine and pseudoephedrine produced about a 30-percent decrease in nasal airway resistance, whereas phenylephrine at 10 milligrams was not

significantly different from placebo.

Now, phenylephrine is a potent alpha agonist and if you administer it by other routes, you actually can see very significant systemic effects. This was a study of cardiovascular of -- cardiovascular effects of cold remedies, comparing 50 milligrams of phenylpropanolamine, 10 milligrams of phenylephrine and placebo in a randomized double-blind crossover design study in patients that were otherwise healthy. And this was done to look at the cardiovascular effects and you can see that the systolic blood pressure and the diastolic blood pressure were significantly elevated with the alpha agonist phenylpropanolamine, which by the way, has a bioavailability of 95 percent, whereas the phenylephrine had no significant difference from placebo.

None of the regimens had an effect on heart rate. There was also other measurements such as total peripheral

resistance et cetera, and the phenylpropanolamine always demonstrated an effect.

So it's demonstrating that it's able to stimulate the alpha-adrenergic receptors both in the nose and also in the systemic circulation, whereas it appears that the concentration of phenylephrine that reaches the blood is not sufficient to stimulate those receptors at 10 milligrams.

Now, I mentioned that phenylephrine is a very potent alpha agonist and anesthesiologists frequently use it as a pressor agent during surgery. And this is a dose response study of IV phenylephrine, again in healthy volunteers. The dosage were between 0.2 and 1.6 milligrams, and this is the plasma concentration of phenylephrine in relationship to systolic and diastolic blood pressure, heart rate, and circulating plasma norepinephrine. As the concentration of phenylephrine in the blood increases, the

blood pressure increases, the heart rate decreases by a barrow receptor reflex and because of this reflex there's a decrease in sympathetic activity, and as a consequence the output of norepinephrine decreases. So phenylephrine clearly has the ability to have potent effects on the alpha receptor, but it has to get there in order to do it.

And this is from the Hengstmann study, the bioavailability that's been quoted from 1982. I looked at just, in this graph, the free phenylephrine since there is an issue about the metabolites being inactive, and if you measure total, you're measuring inactive metabolites along with the active, and they used a tagged phenylephrine.

There were only four patients in the IV study and there were three in the oral that got blood levels, and there was an additional seven, for a total of ten patients that had urinary excretion. This difference in dose-adjusted area under the curve

indicates a 30 percent -- 38-percent bioavailability. If you look at the urinary excretion of phenylephrine it was about 16 percent in the first 2 hours during IV, and 2.6 percent during oral. So I believe someone earlier mentioned that they thought that this was an overestimate of the bioavailability.

Next is Dr. Randy Hatton, who's the co-director of the Drug Information Center at the University of Florida, who did the lion's share of work at retrieving the articles, and along with Dr. Winterstein, conducting the meta-analysis with Dr. Shuster's assistance.

Dr. Nove, if you could double-click on that, please. And he is by telephone if you have questions for him. Modern technology. It will take a second for it to --

MR. HATTON: My name is Randy Hatton and I'll be presenting our paper today on the efficacy and safety of oral

phenylephrine. It was a systematic review and meta- analysis that was published earlier this year in the Annals of Pharmacotherapy.

MR. HENDELES: Can everybody hear it?

MR. HATTON: We attempted to combine the evidence that's available on the efficacy of oral phenylephrine. In order to do this we chose as our primary outcome variable the maximum relative reduction in nasal airway resistance, compared with placebo, over 120 minutes. We considered several other primary outcome variables, including the area under the curve for the change in nasal airway resistance. However, we concluded that this would be too difficult to understand.

We also considered looking at the relative reduction in nasal airway resistance at a specific time point, say 60 minutes. However, this did not allow for variability in the absorption of oral phenylephrine. We

didn't consider looking at the relative effects on nasal airway resistance at several time points after the dosing of oral phenylephrine and placebo. We were looking for a single outcome variable that would best compare oral phenylephrine to placebo, and we felt that measuring it at multiple time points might increase our chances of making a time point error in finding differences by chance.

Therefore, in order to meet our objective, we chose the maximum nasal airway resistance change over 120 minutes as our single variable that would best compare these two agents. The maximum effect on nasal --

DR. TINETTI: We're just trying to get it so that you can see the slides as well as Dr. Hatton.

(Discussion off record)

MR. HENDELES: The panel should have a copy of the slides, so maybe you can just follow along.

MR. HATTON: The maximum effect on airway resistance could occur at different times for placebo and for oral phenylephrine. However, we thought this would be a good outcome measure because we figured an active drug would easily show a greater maximal effect over this short time period of roughly only 2 hours. We felt that that would be actually in fact a sensitive measure of phenylephrine's effectiveness.

We did several secondary analyses. Since the studies varied in their duration -- several of them had collected data for more than 120 minutes -- we wanted to look see at whether the -- if the maximal effect occurred greater than 120 minutes, whether this would change our results. We also wanted to look at the subjective response to oral phenylephrine as measured by nasal symptom scores. These ordinal symptom scales, however, varied from study to study and made it difficult to combine these data.

We also wanted to look at the cardiovascular effects of oral phenylephrine. So we looked at heart rate, blood pressure -- at heart rate and blood pressure. And finally we wanted to look at all these variables for the various doses for oral phenylephrine.

In order to find the data for our meta-analysis, we wanted to use a very broad search strategy. We searched multiple databases from their inception and we included any non-English language information. We also searched for information in the Federal Register, our personal files, and for any references that were cited at any of the papers -- at the end of any of the papers that we identified. We wanted to do a broad search to be very sensitive, to make sure we picked up anything that was out there but we wanted to limit our results to any randomized placebo-controlled trials and exclude any studies that were

combination products.

As we attempted to synthesize the data that we did find, we found that the subjective data on nasal symptom scores were too heterogeneous to do a meta- analysis. So we just simply presented these data in a qualitative fashion. In the original studies, if the authors found a statistically significant difference for oral phenylephrine, we considered these studies to show that it was effective. If there's no significant difference, we considered these to show that it was not effective.

For the objective data on nasal airway resistance, we had raw data available to us, so we calculated the specific change in nasal airway resistance for each patient. For the meta-analysis itself we used a random effects model and for this random effects model, Dr. Shuster will be going into more detail in his presentation.

We did include one parallel study

in our meta- analysis. This parallel study was used in the original FDA review panel, so that was one of the reasons why I wanted to include it. We also wanted to include it because it found a positive effect for oral phenylephrine.

We located 15 studies evaluating the effects of oral phenylephrine on nasal airway resistance. These studies were all completed between 1959 and 1975 and were available for the original 1976 FDA panel. All studies looked at the effects on nasal airway resistance for 120 minutes or more except for one, and it only studied the effects for 60 minutes. It's important to note that there were very limited demographic information provided for each of these studies. Most of these studies were unpublished, so it's difficult to look for any demographic variables that might have contributed to differences in the results of the various studies.

In this figure we present the primary analysis of our study. We identified 8 studies for the 10- milligram dose of oral phenylephrine compared to placebo. And as you can see from these data, there were four studies -- four studies that showed positive effects for phenylephrine and four studies that showed no effect.

If you looked at the pooled estimate on the effect on nasal airway resistance, there was about a 10 percent greater reduction in nasal airway resistance but this effect was not statistically significant. Also it's important to note that we found that these data were very heterogeneous.

In addition to the eight studies used in our primary analysis, we found four additional studies that looked at oral phenylephrine at 10-milligram dose. These studies however did not provide estimates of the variability effect. In order to include

these studies we imputed the variance for these studies. In these four additional studies two were positive and two were negative, and by including this and redoing our meta- analysis we found very little change in the point estimate for the change in nasal airway resistance or the confidence interval.

When we looked at peak effects on nasal airway resistance that could occur at greater than 120 minutes, again, it had very little effect on point estimate or confidence interval. What these analyses showed was that there was roughly a 10-percent greater reduction in nasal airway resistance for oral phenylephrine compared with placebo. However, none of these differences were statistically significant. This begs the question, is a 10-percent reduction in nasal airway resistance for phenylephrine compared with placebo clinically relevant. In our opinion, it is not.

As I stated before, our data were very heterogeneous. We attempted to look for variables that might explain some of this heterogeneity. In this figure that was published in our paper, we looked at the different laboratories that did these studies on oral phenylephrine, and we looked at any possible dose response effects.

As you can see in this figure, the striped bars come from one laboratory, Elizabeth Biochemical, and this laboratory predominated the positive findings for oral phenylephrine. If we put a rough line through all of the Elizabeth Biochemical studies it shows that there was no dose response relationship for the 10-milligram dose, and the 15-milligram dose, 20 milligram, and 25-milligram dose for phenylephrine.

Also it's important to note that for these studies we noticed that the variance for the placebo groups in these

studies was extremely small. If you exclude the Elizabeth Biochemical studies and only look at the other studies that were done, you find that there is an increasing effect with increasing doses.

It's also important to note that the 25- milligram dose, when we looked at the Elizabeth Biochemical studies, the other studies, and if we combine all these studies together, this is the only group -- this is the only dosage, I should say, that the 95 percent confidence interval was greater than zero.

Now I'd like to briefly focus on the subjective results that we qualitatively described in our paper. Please remember that these different studies showed a variety of -- they used a variety of scales to assess nasal symptoms. However, if we ignore these differences, 4 of the 8 of the studies that were done show that phenylephrine at 10 milligram was effective at reducing these

symptoms, whereas only 38 percent or 3 of the 8 of the studies for the 25-milligram dose showed effectiveness for oral phenylephrine.

One of the things we wanted to do in our paper was to look at the differences between the objective measurement of nasal airway resistance and the subjective measurement of nasal symptom scores. In all the studies that we identified, there were 26 objective-subjective pairs. Most of these objective-subjective pairs agreed, 17 of 26, or roughly two-thirds agreed. Of the 9 studies out of 26 that did not agree, in other words, you'd find effectiveness using one type of measurement and not the other, most of these showed effectiveness using -- or 8 used -- showed effectiveness using nasal airway resistance and only 1 showed effectiveness using symptom scores not using nasal airway resistance.

This suggests that nasal airway resistance is a more sensitive measure of

efficacy.

We also did a limited analysis on the cardiovascular effects for phenylephrine and we looked at the different dosages for which we had the raw data, and so we looked at this in the same way we did on the nasal airway resistance where we had the raw data and looked at the individual patient results. This is -- these are the combined results for that, and these show a minimal effect for phenylephrine on heart rate, or diastolic and systolic blood pressure.

What I've highlighted here are the only ones where the 95 percent confidence intervals were exclusive of zero. For the 75-milligram dose of one study, as shown on the last line of this slide, it showed a decrease in heart rate of a negative 7 beats per minute, and an increase in systolic blood pressure of 5.6 millimeters of mercury. This is consistent with the pharmacology of phenylephrine but it's only based on one

study. If you focus on the studies between 10 milligrams and 25 milligram, which we combined several studies, you can see that there was no detectable effect on any of the cardiovascular parameters.

So what do these data show? In our opinion, these data show that the data available do not support the conclusion that phenylephrine 10 milligrams is effective in reducing nasal airway congestion. What these data also suggest is that a higher dose, 25 milligrams for example, may be more effective. It's also important to focus on the fact that the studies that we did combine in this meta-analysis were very heterogeneous. This heterogeneity suggests that there may be methodologic differences among the studies that we combined and more than just random error was going on.

Only one laboratory, Elizabeth Biochemical, provided consistent evidence of positive results for oral phenylephrine. Our

overall estimate may actually be in fact several different estimates that we tried to combine into one. It may be attributed to various factors between the studies. These factors could include unreliable methodologies used by some of the laboratories. It could include differences in the patients included in these various studies. This could be their different disease states for conditions. It also could include genetic variations in the absorption of phenylephrine.

And finally, one possible explanation could be fraudulent reporting of results. Unfortunately, we'll never know which of these explanations or of other explanations contribute to the heterogeneity of the data.

If we focus on these subjective results that are included in this review, they're equally as unimpressive as the objective results on nasal airway resistance.

Also the lack of effects on the cardiovascular system are consistent with no effects on the vasculature. If there's no effect on the systemic vasculature perhaps there's no effect on the nasal vasculature.

So in conclusion, our data support that there's insufficient evidence that phenylephrine 10 milligram is effective, and we would like to support that rigorous, methodologically sound dose-ranging studies are needed to study this issue further.

This concludes my summary of our meta-analysis that was published earlier this year and I'll be glad to answer any questions when the opportunity presents itself. Thank you very much.

MR. HENDELES: Thank you, Dr. Hatton. I think if Dr. Hatton had seen Dr. Koenig's exhaustive presentation, he may have shortened his, because we had a lot of duplication.

Our next presenter is Dr. Jonathan

Schuster, who's a research professor of biostatistics at the University of Florida and he has some comments on the Consumer Health Product Association meta-analysis and the statistical methods they used. And for the panel, there are three tables in Dr. Shuster's handout that he will be referring to.

MR. SHUSTER: -- Florida, Division of Biostatistics, and the College of Medicine. Today I'm going to mainly talk about the Kollar paper, and I'll begin with an executive summary. I'm going to talk about fixed versus random effects meta-analysis. Then I'm going to review the Kollar fixed effect analysis. I will critique the random effects analysis, and I then will reanalyze the random effects meta-analysis in a slightly different manner.

Now, meta-analysis is an attempt to put studies together in a meaningful way. These studies are considered independent and

they have effect size of each one, we want to get some overall measure of effect size. Effects meta-analysis will say all these effect size are one and the same.

A random effects analysis says the following; these effect sizes, from the individual studies, come from some target population of studies. We have a sample of studies and we want to make an inference about the overall effect, the average overall effect, in this target population. These are two very different things but you'll notice that it could happen that you have random effect analysis -- we're still working the fixed-effect case, if you really do have the same number for each effect size.

Now, it is interesting that the Kollar paper -- the data seemed to agree with the Hatton et al. Paper, which by the way, I am a coauthor of that paper, but the words disagree. And so we need to resolve where the differences lie. Our analysis, as

theirs, was restricted to the 10-milligram dose and is restricted to the crossover studies. So we -- there were seven such crossover studies.

Now, looking at these studies I would have a priori, if I was the one doing the original meta-analysis, I would pick a random effects analysis over a fixed-effect analysis and the reason is not that a priori, the effect sizes are homogeneous or heterogeneous, but rather the physical nature of the studies themselves. One thing you'll note though in the paper of Kollar is that there is a large variation in baseline NAR values, about a two-fold in the crossover studies, about a five- fold if you bring in the parallel study that's listed but not used in their analysis.

But also, regional things happen, seasonal things happen that make studies somewhat different, even if they are true replications of the same study. And another

factor is that if the effect size is non-zero, then the fixed effect analysis has to assume they're all the same.

Now, there is some validity to the contention of the authors that a fixed-effect analysis validates that all the effect sizes are zero. However, as a person who thinks in terms of random effects, you would say, well, there are other zeros as well that you can have counterbalancing good and evil, and together, they produce neutrality. So it's a very narrow hypothesis.

Now, I also do not propose to use diagnostic tests of any form to decide. I think you should decide between fixed and random effects on the natures of the studies themselves. I'd like to take -- turn in over to look at the Kollar fixed effect analysis, and I'm going to pull up a table here. In this table, if we look -- I'll guide you through the table -- if you look at the first and second columns, the first column --

DR. TINETTI: It's table M1.

MR. SHUSTER: -- and second column, both have very similar entries both in terms of the width of the confidence interval and in terms of the point estimate. One is only using data from study 2. The other uses model 2B, which takes into account all seven studies. Ten patients in study 2; 113 patients on model 2B.

If you look at the ratio of the width of the confidence intervals, something remarkable comes out. The widths are 87 percent, 84 percent and so on -- and this must have been a typo in the manuscript, 130 percent. In other words, the part is better than the whole. We don't -- there must be something wrong there. And here's the effective sample size in terms of study 2 for the meta- analysis -- 13 versus 10. So those 103 patients, add the effectiveness of 3 patients on study 2, 4, 0, and so on. And one, with the typo, it seems to add negative

4 patients.

So that tells you that they are using study 2 to the virtual exclusion of all the other studies in their fixed analysis.

Now, I am going to now do a little of my own analysis of the 60-minute point in time and that's going to come out as table 2. Okay, in table 2, the effect sizes are as shown in the second column Mraw, or the seven effect sizes, they range from minus 5.6 --

MR. HENDELES: Table 1.

MR. SHUSTER: -- to plus 1.6. And the standard errors, you'll notice vary widely from.74,.36, up to 2.11 and 2.30, so there is a big difference.

Now, if we put together -- believe in a fixed- effect model, what we do is we put these together in weights that are proportional to the inverse of the square of the standard error. In other words, inversely proportional to the variance of the estimator and that's where these weights come

up -- 0.17 for study 1, 0.71, 10 times its natural weight for study 2, and only 1.7 percent for the very largest study, study 7. So it's basically studies 1 and 2 are running the show for the fixed-effect meta-analysis done in this matter, and the overall confidence interval comes out to be very similar to -- in my analysis, to the covariance analysis done by the authors.

Notice that if you use the weights that are inversely proportional to the estimated variance you get a huge significant difference. If you use weights and not the -- just weight each study equally, it still is significant but only marginally. And finally, if you use weights proportional to the sample size, guess what, the significance disappears. It's only less than two standard errors above zero.

Now, let us turn over to the reanalysis of the random effects, and the Kollar, et al. did a mixed model using all

the data without first breaking it down into study-specific effect size. It was very complicated but has some problems with it. It makes a huge number of assumptions relative to those needed, if you just get the effect sizes from the seven studies and then start putting them together, as most meta-analyses do.

They have inherent assumptions within small sampling units, within bigger sampling units, and so on. Normality is assumed, or a Bayesian method has to be assumed in order to get this done, and the population to which the inference is made, I claim, is very poorly defined. You cannot explain what that population is to a layperson.

Now, let's contrast to a method that is -- I've referenced to -- there are two papers that have used this kind of method. What you do is, is you say all right, if you're doing random effects, I'm

going to have a target population of study scenarios. I've got this target population over here and that's, you know, maybe it's the region I'm doing it, the time I'm doing it, you know, what is my treatment and control and so on. Could be -- I could have in there whether it's a crossover study or a parallel study.

Now, over here I've got my designs and my model is -- the target population, I'm going to pull out a study scenario and I'm going to pull out a study design and put them together, okay, and that is going to be my population that I'm making the inference to, okay? The advantage here is that every study is weighted equally. If you start distorting the weights of the study according to the design, well, that doesn't mean the importance of it is -- in the real world, is not related to the design.

And the analog I gave is, you have two congressional districts, let's say

they're equal size, and you sample 1,000 people from one and 100 people from another and you put those together -- really they should be weighted equally, but you're weighting the other one 10 to 1 strictly because someone did more sampling than the others, so you're going to get a bias. It's going to lean towards -- in fact, it leans towards study 2 and their meta-analysis that they did leans towards study 2, okay?

If you do that, we will look at equal weights. You now have a -- you can do this non-parametrically or parametrically. I'll look up -- we'll pull up table 3 to see what this meta-analysis does. We look at that at each time point and we use the effect sizes that are published -- the estimates that are published in the paper.

And look what happens, not a single time point comes out to be significant. Either -- if you want to do it by a t-test which assumes, again for those Bayesian

folks, that you have a normal distribution of effect sizes, or if you do it non-parametrically by a sign rank test, which is closer to what the Follmann and Proschan have done.

Both -- either way, you get no significant difference at any point in time for these studies, and the Hatton study done the same way, no significant difference. So this reanalysis indicates that if you do the meta- analysis by this simple -- taking the effect sizes and putting them together independently, you reach a conclusion that's very different than what was in the other -- in the Kollar paper. And I hope that this -- it probably doesn't, but I hope it resolves the controversies surrounding the meta-analysis but it does not resolve the issue of efficacy.

These studies, as many people have noted, are very small, only 113 patients, done a long time ago. And the fact is that

even though zero effect is consistent with the data there may be other effects that if you draw a confidence interval about it that are -- that's fairly wide and so you cannot conclude conclusively that there is no effect but these data -- the bottom line is these data do not prove there is an effect. Thank you.

MR. HENDELES: So for those of us who are not -- who don't follow statistics easily, what he was saying is that we had the same results except the -- we described it as the glass being half-full and they described the glass as being -- excuse me, we said it was half-empty and they described it as half-full.

I'd like to just briefly cover two of the more recent modern-day Schering studies. Dr. Danzig will be giving all of the details of the study, but I think it's appropriate to look at the pharmacodynamic response. This is the percent change in

nasal symptom scores in the Vienna Chamber.

Patients were randomly assigned in a crossover manner to receive placebo, phenylephrine 12 milligrams rapid release, and pseudoephedrine 60 milligrams rapid release, and you can see quite clearly there was no significant difference between phenylephrine and placebo, but the positive control did show a roughly 20-percent decrease in symptoms.

I would speculate that if you cannot find a difference in a sensitive pharmacodynamic model, it's really unlikely you're going to find a difference in patient's nasal stuffiness in the wild.

In their second study, which was just posted on December 3rd, they compared placebo, phenylephrine rapid release 10 milligrams, and the combination of montelukast and loratadine in a double-blind randomized parallel design in 379 subjects. This is probably the largest sample size to

date, and has the symptom scores that the -- that an NDA would require, except it's in a chamber.

They exposed these patients first before randomizing them to a day where they primed them with the allergen and they selected out only those patients who exhibited a nasal score of two or higher for stuffiness. So these patients all had stuffiness when they came back into the chamber for their treatment.

And you can see here again, the pharmacodynamic response is not significantly different between phenylephrine and placebo, but it was significantly greater for the combination, probably owing to the leukotriene receptor components. Since nasal stuffiness is not mediated by histamine, one would not expect antihistamines to modulate it.

And lastly, if you bear with us for a second, we have a video clip of a recent

Sudafed advertisement from television which I think grossly exaggerates --

(Video played)

MR. HENDELES: So I think there is no question that that grossly exaggerates this non-significant difference between placebo and phenylephrine. Can I have the last slide, please? That's it.

So in summary, oral phenylephrine at a dose of milligrams is no more effective than placebo. In other words, if you have a stuffy nose and you take Sudafed PE, you're going to still have a stuffy nose. It does not cause systemic side effects because it doesn't get into the blood. It has poor oral bioavailability. Clearly appropriate dose-response studies are needed to define the dose of phenylephrine that will give you both relief and minimal side effects.

And lastly, as you can see, the TV ads are grossly misleading. And I would encourage the FDA, if they have the power, to

ask the industry to -- for a moratorium on these ads while these dose-response studies are being conducted. And I thank you, and I will take any questions you have.

DR. TINETTI: Thank you. Does the panel have any -- or at this point, just, again clarifying questions to any of the petitioners?

MR. HENDELES: And Dr. Hatton and Dr. Shuster are on the conference phone and they will be glad to answer any questions that you might have for them.

DR. FOLLMANN: I guess, I --

DR. TINETTI: Please identify yourself.

DR. FOLLMANN: This is Dean Follmann. I have a comment about the choice of endpoints that you use. So you use the maximal benefit for the placebo versus the treatment groups as your endpoint. You gave some reasons why you chose to do that.

The FDA had some comments as to why

they thought it wasn't such a good endpoint. In particular, it was never one of the endpoints of the study to find out priori -- it probably has additional variability than if you measure, say, just at 60 minutes.

But I also think the choice of this endpoint would tend to dampen any treatment effect, and I'll try to explain my reasoning briefly. Let's suppose you did a study where you just measured at 15 minutes, and at 60 minutes, and the drug is effective, and it has a big drop at 60 minutes. So when you take the maximum in the drug group, it's always 60 minutes.

If you go in the placebo group, let's suppose there's no effect whatsoever. And so you take the maximum benefit. Sometimes it will be at 60 minutes, sometimes, it will be at 15 minutes. And so when you compare that difference, it's going to be less than when you compare it at 60 minutes.

So I think this leads to a kind of attenuation of the treatment effect. And if you look at the effect estimates of the consumer health meta-analysis, they get about a 20 percent effect and you get about a 10 percent effect. And I think it might be partly explained by the choice of endpoint.

MR. HENDELES: Would Dr. Hatton like to respond to that?

MR. HATTON: Yes, we could barely hear it, it was very choppy. But I think we got the gist of it. I think if you were to do this, if someone were to do the exact same analysis over and use a, say, 60 minutes, you'd find essentially the same results.

Even though there may be some theoretical reason why you think this may dampen the effect, in reality, the way the data play out at 60 -- if you did a specific analysis at 60 minutes, you would find a 10 percent difference.

DR. FOLLMANN: So did you do that?

Did you do the analysis in 60 minutes?

MR. HATTON: And Dr. Shuster has a comment as well.

MR. SHUSTER: Yeah, in the random effect analysis, there was no significant difference at any time point, even allowing for multiple, you know, the -- choosing a bunch of time points that has the issue of error control, you probably have to do some sort of multivariate method, really, to control it or area under the curve, you can bring it down to one variable, and we thought the area under the curve was a harder thing to understand for the public.

DR. TINETTI: So the answer to that is you did 60 minutes and there still wasn't a difference? I think is what -- what the question was.

MR. HENDELES: Did you hear that Jonathan?

MR. SHUSTER: No, we didn't hear that.

MR. HENDELES: The question is did you do 60 minutes and there still was no difference?

MR. SHUSTER: Yes, yes, we repeated that about minutes. At the 60 minute time point, we did the analysis, there was no difference.

MR. HATTON: Yeah, that is the -- well, we did it at every time point in the random effect.

DR. TINETTI: Thank you, I think we understand. And we're going to move on to another question.

MR. HATTON: I think in a fixed effect, whether you do it and you believe a fixed effect, then you're going to weight the studies inversely proportional to the variance to get the smallest error of -- that's the optimal combination --

MR. HENDELES: Jonathan?

MR. HATTON: And the study too pointed out -- the study to everything in

meta-analysis --

MR. HENDELES: I don't think he --

DR. TINETTI: Can you just turn it off?

MR. HATTON: You could translate to study, too.

DR. NGO: Sir, sir.

MR. HATTON: Other studies --

MR. HENDELES: Dr. Shuster. Hold on. There was another question.

DR. D'AGOSTINO: Ralph D'Agostino, I'm afraid to ask the question.

(Laughter)

DR. D'AGOSTINO: You know, to just go a little bit beyond the question that was just asked. The concern, one of the concerns I have, and it's nothing to do with the sort of bottom-line. But one of the concerns I have is this rush to meta-analysis and going through the gymnastics in terms of describing different meta-analysis.

I mean, for efficacy, we usually

look at the individual studies, and we're completely missing the virtues of some of the studies versus the other studies and, sort of, what this individual studies are telling us. Are you suggesting that meta-analysis is the right way to look at efficacy?

MR. HENDELES: No, no, we're not. And we, actually, in our paper, which should have been appended to this, did look at the individual studies. Dr. Hatton, do you want to briefly comment on that?

MR. HATTON: I'll let Dr. Winterstein who's here, comment, if you don't mind.

MR. HENDELES: Sure.

MS. WINTERSTEIN: So there is -- there was certainly a philosophical problem whether one should summarize studies that show a significant amount of heterogeneity. And once we found that there was heterogeneity, we -- the point of the process to find out what the reason for this is

rather than just aggregating all results.

And unfortunately, the studies don't provide a whole lot of information on the subjects that were included, so it was hard for us to ascertain whether there are really differences in the effect, depending on patient characteristics.

The only attempt we made was -- or the only thing we could do was to look at individual laboratories, and this, Dr. Hatton presented already, in our comparison of the best pharmaceuticals versus the other laboratories. And there is certainly a difference there. Why that is -- is of course not possible for us to ascertain.

The other issue we found was that the studies that showed the positive effect typically had a very small variance on placebo. So essentially, during the placebo exposure, patients didn't show any effect and it was consistent across all subjects. This was different in the studies that showed that

there was a placebo effect, there was much more variance among those.

And this can have various explanations. One might be that the studies that didn't show any placebo effect, consistently across subjects just did have a better measurement. Another idea would be that for some reason, the subjects reacted somehow differently. However, they were picked, there may be differences within subjects, there maybe fraudulent reports, and it's absolutely impossible for us to ascertain.

MR. HENDELES: Dr. Winterstein, the Chair is asking to move on.

DR. D'AGOSTINO: You just -- you know, the studies, in the history of a lot of these studies in the OTC, is there are a lot of failed models in terms of trying different things and they didn't work and then sort of moving to studies that finally did work.

And so, with that, and I'm not

saying that's what happened here, because I really don't know. But to pool all the studies that are submitted, maybe pooling studies that we know -- or the sponsor knew, weren't very useful and the committee also knew that. So I'm really concerned about the meta-analysis. Thank you.

DR. TINETTI: Any other clarifying, just clarifying questions.

DR. NELSON: Yeah, just one -- actually one or two questions. First of all --

DR. TINETTI: Can you just identify yourself.

DR. NELSON: Yeah, I'm sorry, Nelson. On the last slide in Dr. Hatton's -- next to the last slide, you know, we have this discussion. And one of the things that come up, this fraudulent reporting of results. That's an accusation that comes out of the sky as far as I'm aware.

I mean, is there ever -- is the

FDA, is there any issue that's ever been raised about these studies that would even suggest that this should be brought up publicly?

DR. JOHNSON: No, there isn't -- we've never --

MR. HENDELES: He was just listing all the possibilities.

DR. NELSON: Well, yeah -- well, there's a lot of possibilities that I could suggest for the opposite results. And then, next of all, I would like to --

DR. TINETTI: I think for that point, I think we suggest we just ignore that remark.

DR. NELSON: Okay.

DR. TINETTI: There was no basis, and I -- that will not be part of our deliberation.

DR. NELSON: One additional comment. And that was with regards to the advertisement. Is there anything in that

advertisement that is outside the legal monograph that these companies are currently working under?

MR. HENDELES: I'll ask Dr. Johnson to respond to that.

DR. JOHNSON: I'm sorry, can you repeat that?

DR. NELSON: Once again, Nelson. The ad that we just saw; is there anything in that ad that looks to you that's outside the current legal monograph that companies market their product under?

DR. JOHNSON: Without looking at the copy, I couldn't say. I don't think that there is. I don't -- I didn't hear any claims. I'll just look at the team and see if there were any claims made that were out, not inside, I don't think so.

DR. NELSON: Okay, so there's nothing that's at least --

DR. JOHNSON: And I would just point out that we don't regulate OTC

advertising.

DR. NELSON: No, you know, we're well aware of that. But I was just, you know, as FTC.

DR. TINETTI: Thank you, I think we'll move on. The industry presentation will be introduced -- be introduced by Linda Suydam.

MS. SUYDAM: No, thank you. I won't need it, thank you. Good morning, my name is Linda Suydam and I am president of the Consumer Healthcare Products Association. On behalf of the pharmaceutical industry, I would like to thank the FDA, the members of the Nonprescription Drug Advisory Committee, as well as the author of the citizen's petition for raising the issues we are discussing today.

Today, you will from Schering-Plough/Merck Pharmaceutical Joint Venture Company and Schering-Plough Corporation, and from the CHPA industry

taskforce, comprised of members from McNeil Consumer Healthcare, Wyeth Consumer Healthcare, GlaxoSmithKline, Perrigo, Novartis, and Bayer Consumer Healthcare.

We welcome this opportunity for the public review of scientific data and we look forward to an open and productive discussion. Prior to the taskforce presentation, I would like to introduce Dr. Melvyn Danzig and Dr. John O'Mullane.

Dr. Danzig, project director, clinical research allergy/respiratory for Schering-Plough/Merck Pharmaceuticals, will give us a clinical overview of two allergy chamber studies with phenylephrine. Dr. O'Mullane, then will give us, group vice-president, research development for Schering-Plough Corporation will follow with insights into understanding phenylephrine metabolism, pharmacokinetics, bioavailability, and activity. After Doctors Danzig and O'Mullane finish their

presentation, I will introduce the agenda for the industry taskforce presentations.

MR. DANZIG: Good morning. Knowing of the advisory committee's interest in phenylephrine, I'd like to share with you, today, the results of two clinical studies, which measure the activity of phenylephrine in environmental exposure units or chambers.

By the way, we were asked by the FDA to share the data with you today. Synopses of these two studies were distributed to the committee and are posted on clinicaltrialresults.org. Just to note, in the handouts, study 4579 was indicated such, the other handout didn't have the study number, but that is study 4822.

Two studies -- as I mentioned, two studies were done. The first was trial 4579. It was located in Vienna; Professor Friedrich Horak in the Vienna Challenge Chamber did the study. And the second one was in the Environmental Exposure Unit, Kingston General

Hospital, under the auspices of Professor James Day.

What I'd like to do for the rest of my presentation, I'd like to go through the chamber methodology because it may be new to several members of this committee, go through the study design, discuss the results, and when the results come up, I tried my best to keep the placebo results in grey, the phenylephrine results in green, the pseudoephedrine in orange, and loratadine/montelukast in blue. And then I'll have some conclusions. Just to remind everybody that loratadine/montelukast is a fixed-dose combination which is under active FDA review at this time. Just watch the next slide, it's a quick animation. And then I'll go through explaining it to you.

This is the unit, Jim Day in the Kingston General Hospital. Air comes through a series of fans. It goes through the sieving area, room, exhaust fans here that

force some of the air to these fans, which pick up the allergy, the allergen in the fever and circulate it back this way. The rotor rods, which measure the allergen concentration, are located strategically in the chamber.

These are single-dose studies. When the subjects enter the chamber, they are exposed to pollen. Then they are dosed and they are followed for a period of time to evaluate symptoms and other measures, such as air flow. The chamber in Kingston is fairly large, and holds about a 100 to 150 subjects.

The next chamber is the Vienna Challenge Chamber and this is Professor Horak's. He has an enclosed chamber, the airflow is done -- the pollen is -- and the airflow is inside. And you can see some computer stations here where the people from the study staff monitor the subjects inside.

Since this is a smaller chamber that holds about to 16 subjects at any one

time, Dr. Horak likes to do crossover studies, so a fewer number of studies, but better statistical power because of the crossover.

And this is a picture from Jim Day's chamber of subjects taking the pill at the designated time, and here they are exhibiting the symptoms of allergic rhinitis.

(Laughter)

MR. DANZIG: I've attended these chambers; I don't have allergic rhinitis, unfortunately, I took a couple of monitors with me who did suffer from allergy and they lasted about 10 minutes inside the chamber, and had to leave.

Let me review the study subject criteria for both trails. The subjects have to be greater than 15 years of age of either sex and of any race. They have a 2-year documented history of seasonal allergic rhinitis, their skin-prick test is positive to a seasonal allergen. Professor Horak uses

grass in the Vienna Challenge Chamber, because grass is a predominant allergen in Europe. And Jim Day uses ragweed in his unit in Canada.

Subjects come in, as I say, clinically asymptomatic. These studies are done out of the season, so that the season has no conflict with the exposure in the pollen chamber. And in these studies, we do take medical history, physical exam, labs, ECG, vital signs, both to rule out, if any, any exclusion criteria that the subjects may have, and to obtain safety data.

So this is a schematic of the parallel group designed for Jim Day. Subjects come in the screening visits where a medical history is taken, the vitals in the labs. They come in for some priming visits so that they are primed to the allergen, when they come in to the randomization visit, so that we know that when they come in, they will exhibit the symptoms necessary to

qualify.

They come in for about two hours prior to the treatment period and they start scoring their symptoms and measuring their airflow. There is randomization when they become symptomatic. And then they are dosed and they are followed for a 6-to-8-hour period.

Placebo in gray, phenylephrine in green, doesn't show up as well as it does on the PC here, and a comparator. Just with the crossover study, and it's just hard to do a schematic on a crossover with three arms because you have 12 different combinations, every subject receives all three arms and there's a one-week washout between the arms. This part is the same between the studies. And the comparators again, loratadine/montelukast in blue and pseudoephedrine in orange.

In the exposure units or chambers, the subjects assess symptoms in the diary.

They assess the nasal symptoms, nasal congestion, rhinorrhea, nasal itching, sneezing. And I highlight nasal congestion because that was the primary pre-specified endpoint in both of the trials. They also evaluate eye and non-nasal symptoms, tearing, itching -- tearing and itchy eyes, and itchy palate on the 0 to 3 scale. And these are the symptoms included in the FDA-proposed guidance for the evaluation of allergic rhinitis.

What we've been using lately is a peak inspiratory nasal flow meter. This is a unit that each subject can use on their own. It has a face mask, which fits in over the nose and the mouth, and makes a tight seal. The subject is asked to close the mouth and inhale through the meter. And the meter will measure the inspiratory flow.

Actually -- this is actually a mini-Wright meter for those of you who are familiar with asthma, which is inverted. And

there is an ability on the face mask, with the use of just an air syringe, to control the amount of air in the seal to get a tight seal.

Just a note on statistical methodology, and I'm not a statistician. But the symptom data in the PNIF, the baseline value is after exposure in the chamber, prior to dosing. We look at change from baseline averaged over the 4-to-6-hour post-randomization in the chamber, and then, it's for absolute average. And then we look at the time course. And we used an analysis of variance with a treatment effect for the parallel design and including a period effect in the crossover.

So for study 4579, we used pseudoephedrine, a single dose, really, these are single-dose studies, 60 milligrams, phenylephrine 12 milligrams, these were commercially available products, easily -- products that are available in the EU and

placebo.

And here is the time-course results of nasal congestion. Let me just take a minute to go through this. On the bottom is time after dosing. In study 4579, the subjects evaluate the symptoms every 15 minutes in the chamber. So this is the time after dosing. We kept them in for 7-and-a-half hours which is a pretty long time plus the 2 hours pre treat, it's 9-and-a-half hours. That was a long time to keep them in the chamber.

And this is the change in base, change in scores from baseline; going down is better. At the baseline scores, a maximum of 3, 0 to 3 scale, the average was about 2.2. And this was the sample size in the crossover. There was one subject who just took the pseudoephedrine dose and for administrative reasons did not complete the trial.

So from the time of dosing, you can

see an effective pseudoephedrine over the time course in the chamber where phenylephrine and placebo had no effect. If you look at the mean over six hours, this was the primary pre-specified endpoint, as Dr. Hendeles showed the slide, there was statistical significance of pseudoephedrine over placebo and phenylephrine was not statistically significant over placebo. Again, this is just the average of each of the time points over the 6-hour time point.

Now, the peak nasal inspiratory flow; different than the congestion, where down is better, this is up is better. So this is a change from the baseline in the peak nasal inspiratory flow, which was done every 30 minutes.

And as you can see, pseudoephedrine had, patients showed an increase in their flow whereas phenylephrine and pseudoephedrine -- phenylephrine and placebo, I'm sorry, patients tracked each other.

These were the baseline scores on the peak nasal inspiratory flow.

4822 was the parallel group study. The treatment arms included loratadine/montelukast tablet, a PE 10 milligrams Quick Dissolve Strips, these were commercially purchased and matching placebos. And again, the same time-course slide.

The combination of L/M showed a decrease in, or improvement from baseline and nasal congestion, whereas phenylephrine and placebo tracked each other. The pre-specified endpoint, which is a score over the 6-hour average, again showed L/M to be statistically significant over placebo and phenylephrine did not.

Just to note, which I forgot to mention at the other slide, these are the baseline scores. As you can see, ragweed is probably more potent. I shouldn't say probably, is a more potent allergen. You do get higher baseline scores.

And this is the peak nasal inspiratory flow results. The baseline, the flows were lower than the other study, again, ragweed being a more potent allergen. And going up is better, loratadine/montelukast combination showed an increase in flow, and phenylephrine and placebo tracked each other.

So the conclusions we come up with, a single dose of pseudoephedrine showed the expected decongestant response and symptoms in airflow compared to placebo. A single dose of phenylephrine showed no decongestant response compared to placebo, replicated into two studies. And a single dose of loratadine/montelukast versus placebo showed an effect on nasal congestion.

If it's all right with the Chair, I would like to have some clarifying questions if that's all right with you here.

DR. TINETTI: I think what -- we'll do all the clarifying questions -- I think, maybe have the two from -- you'll then be

able to clarify questions --

MR. DANZIG: Then with the clarifying questions for me. So let me introduce John.

MR. O'MULLANE: Madam Chair, members of the committee, I'm speaking on behalf of Schering-Plough Consumer Healthcare, a division of Schering-Plough Corporation. And I'd like to take you through our understanding of phenylephrine metabolism, biopharmaceutics, bioavailability, and activity.

The data I'm presenting today is part of an ongoing development program to produce products based on the pharmacokinetics of phenylephrine. We became aware of this NDAC meeting and worked in collaboration with the FDA to bring our data to this meeting.

In the development program, we needed to understand three things. Firstly, the metabolism and activity of the conjugates

so that we measured the appropriate moiety in blood; secondly, the bioavailability of the active moiety; and thirdly, to determine whether there are opportunities to optimize the bioavailability of the active molecule in blood.

So first of all, I'm going to talk about metabolism and activity. As already been mentioned this morning, phenylephrine undergoes pre-systemic conjugation in the small intestine to produce principally the sulfate and the glucuronide species and all three species are found in the plasma.

So what occurs in practice? So a dose of phenylephrine taken by mouth diffuses through the gut wall where it undergoes metabolism in the gut wall to produce the sulfate and the glucuronide. Those species diffuse into the portal vein and are transported to the liver where they undergo additional deamination and metabolism.

The principle deaminated species is

3- hydroxymandelic acid and that's important to remember because I'm going to be referring to that in my next slide. And the other conjugates are found in the blood here.

So in order to make a reasonable approximation of what's happening as a result of this, we need to understand the activity of the conjugates. And in order to characterize the pharmacokinetic profile, you need to measure the active moiety.

So we went about understanding that, 3- hydroxymandelic acid is actually available commercially. The two other conjugates are not available; we synthesized those, purified them, and characterized those in our Schering-Plough research institute laboratories.

And we tested them for activity in the following assays of relative drug potency, which is the alpha- adrenergic receptor binding affinity assay and then the measurement of activity, both by calcium flux

and the GTP- gamma-S assay.

Here's the summary of the activity results and this may appear to be very crowded, but I'm going to simplify it for you. These are all the receptor assays that we measured and here are the molecules that we are measuring the activity of. Here is phenylephrine; here is the O-sulfate, the glucuronide, and here the hydroxymandelic acid. And as you can see quite clearly, there is no activity for any of the conjugates; all of the activity resides with the parent phenylephrine.

So what about the pharmacokinetics? Well, it's -- we had to step back a little bit here because the basis on which phenylephrine salts were recently approved in the monograph was by a method that relied on taking the plasma samples, subjecting them to enzymatic cleavage of the conjugated phenylephrine, extracting the phenylephrine and then measuring the total.

That of course, based on the results that we have, is an incorrect way of measuring this, we should indeed just measure the unchanged or parent phenylephrine. And so our method relied on taking plasma samples, not subjecting them to any cleavage, extracting out the phenylephrine, and measuring the unchanged phenylephrine in plasma.

So the pharmacokinetics study was conducted in male and female volunteers. Phenylephrine was dosed as an immediate release 10 milligram tablet. Both total phenylephrine and parent phenylephrine were measured in the plasma and here are the results.

After a single 10 milligram oral dose, you can see that our levels of total phenylephrine are around -- are in the order of 60 nanograms per milliliters, and I believe that's consistent with what's been presented earlier. Whereas, if you can see

for parent phenylephrine, it's about 0.6 nanogram per milliliter, and again, I think that's consistent with what's been presented earlier.

If I present -- if I represent those both on the same axis, you can see that the total phenylephrine is here and the parent phenylephrine is hardly visible on the scale. This indicates that following a 10 milligram oral dose, phenylephrine or parent phenylephrine represents less than one percent of the total phenylephrine found in plasma and of course, that is the active moiety.

So we said about trying to understand -- is it possible to increase the bioavailability of parent phenylephrine. And the way that we did this was to really optimize the physiology of the gastrointestinal tract. And here is a diagram of the gastrointestinal tract showing the stomach, the duodenum, jejunum portions,

ileum, ileocecal junction and then into the colon.

If you look at the relative residence time of materials in the gastrointestinal tract, you will see that materials roughly are in the stomach for about half an hour, in the small intestinal area for a couple of hours, and in the colon for about 20 hours.

And generally, it's understood also that metabolism; particularly conjugation is less in the colon, even though it has a greater residence time, metabolism is less, but also the surface area for absorption is less, so those balance out.

So what did we do, we used what's called the Enterion capsule, and -- that isn't actually the size of it. The capsule is this size.

(Laughter)

MR. O'MULLANE: And this is administered to male and female subjects and

it passes through the stomach, through the small intestine. And when it reaches the ileocecal junction, we can -- there's a radiometer device in the cap here, and we can see exactly where it is. When it reaches the colon, we then activate the capsule as follows.

A piston releases the drug into the lumen of the colon so you know precisely where the phenylephrine is being delivered. This was a sequential crossover design and we analyzed the samples with total phenylephrine and parent phenylephrine to improve our understanding. And these are the results.

For total phenylephrine, you can see here, this is the oral dose and this is the dose administered into the colon. For the parent phenylephrine, this is the immediate release dose, and here is the dose released into the colon. It may not be obvious from these charts, by the relative bioavailability, when delivered into the

colon is about three fold.

This result here, for the total phenylephrine, suggests and really confirms that there's far less metabolism in the colon. And what's quite interesting is that if you deliver it into the colon, you can see that you can get extended amounts of parent phenylephrine into the bloodstream and they remain there for an extended period of time. So it seems to us that it's a matter of getting it into the bloodstream that is the key issue to address.

So from the conclusions of our colonic absorption study, parent phenylephrine bioavailability has increased about 300 percent when phenylephrine is delivered into the colon. Sustained parent phenylephrine plasma levels are observed up to 24 hours when phenylephrine is colonically delivered. And we, our overall conclusion is that higher overall parent phenylephrine levels are possible by delivering

phenylephrine to specific regions of the gastrointestinal tract.

So what's our overall conclusions? We conclude that parent phenylephrine is active in, in vitro activity assays of drug potency, whereas the conjugates are not active in the same assays.

Parent phenylephrine is the most appropriate market to characterize the pharmacokinetics of phenylephrine. And even though the value of 38 percent that is often quoted in the scientific literature may be correct for total phenylephrine, the actual amount of the active drug is far less than that around 0.38 percent or less.

And exposure to parent phenylephrine may be optimized by drug delivery systems that rely on absorption at other parts of the gastrointestinal tract. And with that point, I conclude.

DR. TINETTI: Thank you. I certainly hope you're not suggesting what I

think you're suggesting.

(Laughter)

DR. TINETTI: Any clarification questions. And I had -- just had a very quick clarification question for Dr. Danzig. The studies you presented, I presume, but can you let us know for sure, are they part of an application for a new drug, application for the loratadine/montelukast?

MR. DANZIG: Yes.

DR. TINETTI: Okay, and do you have comparison of the -- of that drug against the pseudoephedrine? You presented us against the phenylephrine. I don't need to see it. I just wanted to know do you have it?

MR. DANZIG: I mean, the data is under active review of -- by the FDA, and we really had to talk about phenylephrine today --

DR. TINETTI: Okay, I just wanted to know if -- I don't need the results.

MR. DANZIG: And not

pseudoephedrine.

DR. TINETTI: Okay, thank you.

MR. DANZIG: Not pseudoephedrine.

DR. TINETTI: Okay, thanks.

MR. DANZIG: And not in L/M.

Thanks.

DR. TINETTI: Okay.

DR. TAYLOR: Robert Taylor, to Dr. Danzig. Were the treatments blinded in the Ontario studies? And was the sequence of the three treatments randomized to the subjects?

MR. DANZIG: Yeah, so in the Ontario study, the treatments were blinded. There was a placebo to the L/M and there was a placebo to the phenylephrine. And all studies were randomized.

MS. PARKER: This is also to Dr. Danzig.

DR. TINETTI: Dr. Parker, just remember to introduce.

MS. PARKER: Dr. Parker, okay, Ruth Parker. I'm assuming the doses, the 12

milligrams of the phenylephrine and the 60 milligrams of the pseudoephedrine that were used in the comparison must be equivalent. I mean, why not 30 milligrams of the pseudoephedrine.

MR. DANZIG: That's a good question.

MS. PARKER: And do you have anything that could tell me anything about using a -- and I assume, you don't, or you would have presented it, you didn't use any higher dose than the 12 milligram. Do you have any data on any of that?

MR. DANZIG: No, what -- no, well, we went to the monograph and the monograph said 60 milligrams of pseudoephedrine every 4 to 6 hours, or every --

SPEAKER: Four to six hours.

MR. DANZIG: Every 4 to 6 hours and 10 milligrams of phenylephrine every 4 to 6 hours. And that's how we chose the dose. Every four hours, okay. There are better

experts than -- so.

DR. FITZGERALD: I'm sorry, Garret Fitzgerald, for Dr. O'Mullane. I wonder if you have any data that relates the Cmax of the parent compounds, that concentration attained either after 10 milligrams and after 20 milligrams, and how that concentration of phenylephrine relates as far as vascular contractility is concerned, in vitro, or can be extrapolated onto the plasma concentration response curves with parenterally administered phenylephrine, which demonstrates a rather steep dose-response relationship with blood pressure.

MR. O'MULLANE: That wasn't the purpose of our study.

DR. FITZGERALD: I know that.

MR. O'MULLANE: And it would be -- not for me to speculate on that, although, I do see from some pre- printing of materials that that may be addressed in the further CHPA presentation.

DR. GRIFFIN: Yeah, Marie Griffin. Just wondering, based on your study, would there be patient populations that would have, sort of, a more differential absorption, short-gut syndrome, or would you expect that there may be people that don't absorb much of the gut -- in the small bowel?

MR. O'MULLANE: I think it would be fair to say that there is a highly variable absorption of phenylephrine. It's not something that we could, again, speculate from the small numbers that looked we looked at in the study. But there certainly seems to the potential for optimization of delivery, you know, through various regions of the GI tract, and that's about all I can say.

MR. OWNBY:: Dennis Ownby, I had a question for Dr. Danzig and the basis for this question is that the effectiveness of some of these drugs that modulate blood flow through the nose may depend on how long the

nose has been congested beforehand, because of tissue edema. I didn't quite follow how many pre-challenges to sensitize the patients occurred before they went into the chamber and what that time period was like.

MR. DANZIG: Yeah. The priming visits are individualized based on the patient. So both Dr. Horak and Dr. Day bring a cohort of the patients in, expose them in the challenge unit. And if they are able to reach a certain symptom set in the first challenge, then they qualify. If not, they continually bring them back and prime them until they reach a symptom set. If they don't reach the symptom scores that we require, they do not bring them back for randomization.

So again, it's individualized, it could take a subject, one session or four or five sessions. And from clinical practice, you know, that that could -- some subjects respond quickly to pollen and some don't.

MR. OWNBY:: So just a follow-up, that's how they get away with the single dose in the chamber of getting everyone to respond some, because there is normally a very board range of responses to challenge.

MR. DANZIG: Yeah.

MS. PARKER: One more.

MR. DANZIG: Okay.

MS. PARKER: Just one other question about whether or not you had data on heart rate response to the 12 milligrams --

MR. DANZIG: Yes.

MS. PARKER: Versus the two others arms or blood pressure. I think you said you measured it. I'm just curious what the data were.

MR. DANZIG: Yeah, we do, we do -- we do have it. But single dose studies in the chamber really don't pick up anything. People are too busy doing other things.

DR. NELSON: All right, just a couple of quick ones. Was the phenylephrine

--

DR. TINETTI: Just identify yourself.

DR. NELSON: I'm sorry, yes, I apologize. Nelson, sorry, I don't mean to be rude. Was the phenylephrine analyzed before you did the study? I noticed it was -- it was purchased outside the U.S.

MR. DANZIG: The phenylephrine was a commercial product bought in the UK.

DR. NELSON: Okay, and can I ask, was the efficacy of the phenylephrine versus placebo or a comparative part. Was that a primary or secondary analysis point, or was it just something that just was in there.

MR. DANZIG: The primary pre-stated endpoint for the 4579 was the L/M versus placebo and for the second trial, the crossover with phenylephrine versus placebo.

DR. NELSON: Yeah. And one additional question, is there any -- are there any studies with negative chamber

studies, such as you've done, yet positive what you call field studies or outpatient clinical studies. Is there any precedent to that?

MR. DANZIG: Let me answer that by first saying that I had given out two handouts by Professor Day and Professor Horak explaining the chamber model and what it is. And, you know, I'm not aware of all the totality of data that's sent into the FDA. And I'm not able -- maybe, the -- you know, there are other experts that can tell you, based on other drugs, whether or not that could happen.

DR. TINETTI: Does anybody know that question -- the question is the correlation between the chamber and real life experiences with SAR. Does anybody know?

MR. CHOWDHURY: I'll take this question, my name is Badrul Chowdhury, I'm with the division of pulmonary and allergy drugs, I'm the division director there. In a

general sense if you look at the totality of datas of all of these drugs, they usually correlate as far as positives in both situations goes. But there are exceptions and the exceptions where the chamber study is negative and the real-life study is positive, and they are there.

DR. TINETTI: All right, move on. Go ahead, Susan.

DR. JOHNSON: I'd just like to make a couple of comments about 4822 in response to Dr. Ownby's question. I think that there were up to six challenges allowed prior to enrollment. And in addition, what we saw reported were mean scores at the time of the enrollment, so, in the range of 2.75-2.82. But patients were required to have only minimal congestion in order to be enrolled. That was the criteria that they had to meet. So while the mean may reflect generally what the population looked like, not everybody had more than minimum congestion.

And then, I'd just like to make one question for how these studies were done. One of the things that we've been interested over -- looking at these studies over time is the formulation used. And I noticed that there is quite a bit of difference amongst these studies.

So while 4822, the Canadian study looked at quick dissolve strips, which might have introduced some questions about how to blind that study, there were tablet formulations used in the PK studies. And my question is the Enterion capsule, does that involve an actual tableted formulation that may have to dissolve or is that the actual drug substance?

MR. O'MULLANE: It's the tableted formulation which is then crushed into a form micronized, so that it's rapidly released.

DR. JOHNSON: So potentially, more bioavailable, just because it doesn't have to dissolve in --

MR. O'MULLANE: Yes, so that it wouldn't -- I mean, normally, for a drug to dissolve in the stomach, it has that harsh environment in the stomach where you would expect to have the churning and the breaking up of the tablet. So it's really to mimic that kind of effect that you wouldn't otherwise have within the colon.

MS. SUYDAM: Thank you, Dr. Danzig and Dr. O'Mullane. At this time, I'd like to provide you with an overview of the CHPA industry taskforce presentation. As I mentioned earlier, the taskforce is composed of McNeil Consumer Healthcare, Wyeth Consumer Healthcare, GlaxoSmithKline, Perrigo, Novartis, and Bayer Consumer Healthcare. We agree with the citizen's petitioner that providing medicines with an optimal safety and efficacy profile is the top priority.

We're here today to address the petitioner's request to make changes to the monograph to the oral form of phenylephrine.

The petitioner has requested an increase of single-dose phenylephrine hydrochloride from 10 to 25 milligrams. The petitioner also recommends that additional studies be conducted to validate that a 25 milligram dose is more efficacious and as safe, as a 10 milligram dose.

We are following, in our presentation, the FDA's policy decision to defer any discussion on pediatric use. And therefore we will not be presenting any information on the pediatric use of phenylephrine today.

We disagree with the citizen's petition. Phenylephrine 10 milligrams, is an appropriate over-the- counter dose for the temporary relief of nasal congestion. We will review data from multiple studies that demonstrate that 10 milligrams is a safe and effective dose.

We also disagree with the petitioner's specific recommendations to

increase the over-the-counter phenylephrine dose to 25 milligrams. We believe that increasing the phenylephrine dose to 25 milligrams every four hours is not recommended because at this time, there are not sufficient data to prove that the higher dose would have a more favorable benefit-risk ratio.

While there are multiple double-blind randomized placebo-controlled positive studies for both objective and subjective endpoints, we acknowledge that existing studies do not meet all of today's standards for clinical trials. We will add to the body of evidence supporting phenylephrine 10 milligrams by working with the FDA. But let's keep in mind that behind the science, are real patients with real needs and very troublesome symptoms.

In fact, nasal congestion is considered to the most bothersome and difficult to treat of the symptoms of

rhinitis. Nasal congestion associated with acute and chronic rhinitis is a universal experience affecting millions of Americans every year. Nasal congestion is a symptom experienced by the general population resulting from a variety of causes, mostly from common colds and allergies.

For consumers who suffer from nasal congestion, phenylephrine 10 milligrams offers effective temporary relief and has its place in today's market just as it has for the last few decades. Phenylephrine has a long history in both prescription and over-the-counter medicines. In the U.S., phenylephrine hydrochloride was found generally recognized as safe and effective in the OTC monograph finalized in 1994.

It's worth noting that phenylephrine 10 milligrams has also been approved by regulatory agencies in countries outside the U.S., including Canada, Australia, and several European Union

countries.

Data demonstrate that phenylephrine hydrochloride 10 milligrams is a safe and effective dose, and concluded by an FDA panel of experts, very similar to this panel of experts, in 1976. Since 1996, phenylephrine has been widely used in the United States with more than 5 billion dosage units distributed.

We will now hear from the CHPA taskforce representing the 7 companies I mentioned earlier. Dr. Ed Kuffner, senior director of medical affairs in McNeil Consumer Healthcare will summarize the safety data from controlled clinical trials with phenylephrine and post- marketing safety databases. His presentation will also include a review of adverse events associated with higher phenylephrine doses.

Dr. Cathy Gelotte, senior director of clinical pharmacology at McNeil Consumer Healthcare, will present the pharmacology of

phenylephrine and specifically discuss the latest pharmacokinetic data.

Dr. Ken Dretchen, professor and chair of the Department of Pharmacology at Georgetown University will outline the efficacy of phenylephrine 10 milligrams. In his presentation, Dr. Dretchen will review the individual trials that studied phenylephrine 10 milligrams, the two recently published meta-analyses.

And in conclusion, I will present a summary of our findings. Without further delay, I now turn the podium over to Dr. Kuffner.

MR. KUFFNER: Good morning, I'm Ed Kuffner; I'm a medical toxicologist and senior director of medical affairs at McNeil Consumer Healthcare. I'm going to review some of the data with respect to adverse events in vital signs, including pulse and systolic blood pressure that were reported in clinical trials for phenylephrine 10

milligrams. I will also present a comparison of adverse events between phenylephrine 10 milligrams and 25 milligrams.

Spontaneously reported adverse events from combined post-marketing safety databases of the majority of companies that distribute over-the-counter oral phenylephrine in the United States were reviewed. Adverse event reports from member companies of the phenylephrine taskforce were given to the Rocky Mountain Poison and Drug Center for a combined and independent analysis. I'll present the results of this analysis.

Most of the placebo-controlled clinical trials reported safety data, meaning; reporting of adverse events, if they occurred, and documented changes in vital signs if they occurred. There are clinical trial safety data on more than 850 subject exposures from clinical trials in which different doses of phenylephrine were

administered. There are more data on adverse events and vital sign effects for phenylephrine 10 milligrams than for any other dose.

In this table, you see the four studies in which adverse events occurred, and were reported for the 10 milligram dose. In the first column, you see the specific studies, in the second column, you see the rate of adverse events for phenylephrine 10 milligrams and in the last column you see the rate of adverse events for placebo. In each of the individual trials, and overall, the incidence of adverse events with phenylephrine and placebo is low and similar.

On the next slide, I will present data from the only study in which adverse events at a 10 milligram and a 25 milligram dose were reported. In the table across the top row, you see the rate of adverse events for placebo and different doses of phenylephrine studied. The specific adverse

events are listed below in the first column.

The overall incidence of adverse events with the milligram dose was higher than that for the 50 milligram dose, the 10 milligram dose, and placebo. For both placebo and phenylephrine 10 milligrams, the rate of adverse events was 12.5 percent. For phenylephrine 25 milligrams, the rate was 81.3 percent.

As you can see in the table, the specific reported adverse events do not appear to be serious. From this study, in which a comparison between the adverse events of 10 milligrams and 25 milligrams could be performed, it appears that adverse events may be dose related. On the next slide, we will review the vital sign changes with phenylephrine 10 milligrams.

In the column on the left, you see the differences between phenylephrine 10 milligrams and placebo. Across the top row, you see the number of studies reporting data