UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MEETING

TUESDAY, DECEMBER 9, 2003

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The Advisory Committee met at 8:00 a.m. in the Ballroom of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Jeffrey Borer, Chairman, presiding.

PRESENT:

JEFFREY S. BORER, M.D.	Chairman
PAUL W. ARMSTRONG, M.D.	Member
BLASE A. CARABELLO, M.D.	Member
SUSANNA L. CUNNINGHAM, Ph.D.	Consumer Rep.
ALAN T. HIRSCH, M.D.	Member
JOSEPH KNAPKA, Ph.D.	Patient Rep.
BEVERLY H. LORELL, M.D.	Member
STEVEN E. NISSEN, M.D., F.A.C.C.	Member
THOMAS PICKERING, M.D.	Member
EDWARD PRITCHETT, M.D.	Consultant (Voting)
RONALD PORTMAN, M.D.	Member
DORNETTE SPELL-LESANE, M.H.A.,NP-C	Ex. Secretary

SPONSOR PRESENTERS:
LUIZ BELARDINELLI, M.D.
EUGENE BRAUNWALD, M.D., F.A.C.C.
PETER KOWEY, M.D., F.A.C.C.
JEREMY N. RUSKIN, M.D., F.A.C.C.
MICHAEL SWEENEY, M.D., F.R.C.P.
ANDREW A. WOLFF, M.D., F.A.C.C.

FDA REPRESENTATIVES:
ROBERT TEMPLE, M.D.
DOUGLAS THROCKMORTON, M.D.

AGENDA ITEM **PAGE**

P-R-O-C-E-E-D-I-N-G-S

8:01 a.m.

CHAIRMAN BORER: This is an FDA Advisory Committee and we don't have the FDA representatives here yet to advise, so we'll wait a few more minutes. The advisees have arrived. Glad you could join us, Doug.

DR. THROCKMORTON: Always glad to be here.

CHAIRMAN BORER: Okay. We will begin. Today is the second day of this meeting. The Committee will discuss the new application, a New Drug Application, NDA 21-526, CV Therapeutics, proposed trade name Ranexa, generic ranolazine, 375 milligrams and 500 milligram tablets for prevention of chronic stable angina. The Executive Secretary Dornette Spell-LeSane will read the Conflict of Interest statement.

SECRETARY SPELL-LESANE: Good morning. The following announcement addresses Conflict of Interest issues with respect to this meeting and is made a part of the record to preclude even the appearance of impropriety at this meeting. I can't

say that word. The Conflict of Interest Statutes prohibit special Government employees from participating in matters that could affect their own or their employer's financial interests.

All participants have been screened for conflicts of interest in the competing products and firms that could be affected by today's discussion. The Food and Drug Administration has granted waivers to the following individuals, because it has determined that the need for their services outweighs the potential for a conflict of interest: Ronald Portman, M.D., has been granted a waiver under 21 USC Section 355(n)(4), amendment of Section 505 of the Food and Drug Administration Act, for ownership of stock in a competitor.

The stock is valued at less than $5,001. Because the value of the stock falls below the de minimis exemption allowed under 5 CFR 640.202(a)(2), a waiver under 18 USC 208(b)(3) is not required. Dr. Portman has been granted a waiver under 18 USC 208(b)(3) for a consulting contract with a competitor through his employer. He receives less than $10,001

annually.

Paul Armstrong, M.D., has been granted a 208(b)(3) waiver for speaking and consulting for a competitor on unrelated matters and for serving on a competitor's data safety and monitoring board on unrelated matters. He receives less than $10,001 annually from each. In addition, also waived is his employer's grant from a competitor to study an unrelated product. The grant generates between $100,001 and $300,000 a year.

Jeffrey Borer, M.D., has been granted a 208(b)(3) waiver for his consulting for a competitor on unrelated matters. He receives between $10,001 to $50,000 annually.

Edward Pritchett, M.D., has been granted a 208(b)(3) waiver for his consulting for a competitor on unrelated matters. He receives between $10,001 to $50,000 annually. He has also been granted a waiver under 21 USC Section 355(n)(4) for ownership of stock in a sponsor of a competing product. The stock is valued between $5,001 to $25,000. This interest is not included in his 208(b)(3) waiver, because the

value of the stock falls below the de minimis exemption allowed under 5 CFR 640.202(a)(2).

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. In the event the discussions involve any other products or firms not already on the Agency for which an FDA participant has financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

CHAIRMAN BORER: Thank you very much. Introductory comments from Doug Throckmorton will not be presented, because he doesn't have any. Therefore, we will begin the sponsor presentation.

DR. SWEENEY: Thank you. Good morning, Mr. Chairman and Committee members. My name is Dr.

Michael Sweeney. I'm vice president of Medical Affairs at CV Therapeutics. I will present a brief outline of the presentations this morning to orient the Committee to its presentations which will provide more detailed data later.

First, on behalf of CV Therapeutics, I would like to thank the Committee and the Agency for the opportunity to present data on ranolazine or Ranexa, which we believe represents the first novel therapy for angina in 25 years. As described in both CVT and the FDA's briefing documents, Ranexa has shown to be effective in the treatment of angina in patients with severe coronary artery disease. Ranexa achieves this by a unique pharmacodynamic profile, which does not depend on changes in heart rate, blood pressure or contractility, unlike existing therapies to treat angina.

Ranexa offers the potential to be complimentary treatment to existing agents, particularly where the patient's hemodynamics or concomitant diseases limit the use of these agents. This morning we will present data which demonstrates

that the extensive Ranexa Development Program addresses the issues raised by the Agency. Today, we seek the Committee's support for the approval of Ranexa for the treatment of chronic angina in patients with severe coronary artery disease as functionally defined by severe angina pain and impairment of exercise tolerance.

The proposed initial dose will be 500 milligrams twice daily upwardly titrated to 750 or 1000 milligrams twice daily depending on patient response and tolerability. Today, the Committee is tasked with balancing the quantifiable measures of benefit, anti-anginal and anti-ischaemic efficacy, achieved with minimal hemodynamic effects and as demonstrated during the Ranolazine Development Program, the fact that it is well-tolerated, with the adverse effects and the theoretical risk of torsade due to prolongation of the QTc interval.

Prolongation of the QTc interval is not the sole determinant of a dose propensity to cause torsade. Dr. Luiz Belardinelli will describe in detail an approach to assessing the pro-arrhythmic

potential based on evolving new science that, when integrated with clinical findings, provides a better indicator of the actual risk of torsade. Both CVT and the FDA agree that Ranexa is associated with a small increase in the duration of cardiac repolarization.

To definitively characterize this effect, CVT has undertaken a comprehensive clinical and preclinical electrophysiological assessment of ranolazine. There is a small mean increase of 2 to 3 milliseconds in QTc at normal doses and up to 20 milliseconds under conditions of maximal metabolic inhibition with cytochrome P450 3A4 inhibitors, its predominant metabolic pathway. The conclusion of this comprehensive clinical and preclinical electrophysiology is that Ranexa is fundamentally different to all drugs which cause torsade.

In particular, Ranexa does not lead to early afterdepolarizations, the recognized trigger for torsade, nor does it increase the dispersion of intramural ventricular repolarization, the recognized substraint for torsade. In fact, ranolazine reverses these effects when produced in the laboratory by other

drugs known to cause torsade. As a consequence, Ranexa has a very low potential to cause torsade, further evidenced by the fact there is no reported cases of torsade in the Clinical Development Program.

CVT has prepared a detailed presentation this morning focused on questions asked of the Committee by the FDA. To commence our presentation, Dr. Eugene Braunwald, from Brigham and Women's Hospital in Boston, will describe the unmet need for the treatment of angina patients and how persistent angina continues to impact the lives of patients despite current therapies and despite revascularization. Dr. Andrew Wolff, from CVT, will then describe the efficacy and safety data for Ranexa.

Prior to the discussion of electrophysiology by Dr. Belardinelli and by Dr. Wolff, Dr. Peter Kowey, from Lankenau Hospital, Philadelphia, will place into context the utility of the new science to evaluate pro-arrhythmic effects of drugs preclinically in the absence of reliable clinical predictors for pro-arrhythmic effects. And finally, Dr. Jeremy Ruskin, from Massachusetts

General, will summarize the risk benefit for Ranexa and to look at its possible place in the therapy of angina.

In view of the groundbreaking nature of much of the data which will be presented by CVT, we have asked a number of independent experts in addition to the speakers, who have advised CVT, to attend, to be available to answer the Committee's questions and provide further clarification. Our guests include Dr. Charles Antzelevitch, Dr. John Camm, Dr. Bernard Chaitman, Dr. Gary Koch, Dr. Samuel Lee, Dr. Marek Malik, Dr. Craig Pratt, Dr. Dan Roden and Dr. Peter Stone.

I would now like to hand over to Dr. Eugene Braunwald of Brigham and Women's Hospital to describe the current unmet need for the treatment of angina. Dr. Braunwald?

DR. BRAUNWALD: Good morning. I think all of us in this room realize that angina pectoris remains a serious and frequently disabling condition, despite currently available therapies. Now, angina was first described by William Heberden in 1772, and

his description is really quite accurate today, and it is useful to reflect on his exact wording. It would be "There is a strong disorder in the breast. The seat of it, and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris. Those who are afflicted with it are seized while they are walking with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to continue or increase."

So in other words, angina pectoris has been recognized for more than two centuries as the heart's cry for energy and the drugs we have available, the treatments that we have available are really a response to that cry. Now, there have been many developments in the treatment of angina, but despite the use of traditional anti-anginal agents, beta blockers, calcium blockers, nitrates, as well as revascularization procedures, the American Heart Association estimates that there are more than 6.5 million Americans who continue to suffer with angina pectoris.

Despite these therapeutic advances, it is estimated that 13 million episodes of angina occur each week and that translates into about 1,000 episodes every minute. On average, patients treated for angina experience two episodes daily, making this a major and significant problem. So the improvement in the treatment of angina is an important medical goal.

Now, patients with angina frequently have comorbid illnesses, and in one VA population it was shown that about a quarter to a third have diabetes mellitus, about 1 in 5 have obstructive pulmonary disease, a quarter have peripheral vascular disease and about 1 in 5 also have congestive heart failure. So angina remains a problem, as I have said, despite contemporary drug therapy. Pepine has reported that despite the use of anti-anginal agents, that is beta blockers, calcium antagonists and nitrates, patients still report an average of two attacks a week.

Now, a significant percentage of patients, especially those with comorbidities, can't tolerate the full doses of beta blockers, calcium channel

blockers and nitrates. Beta blockers and calcium blockers have similar depressive effects on blood pressure, heart rate and AV nodal conduction. Clearly, something else is needed, and it would certainly be desirable to develop an anti-anginal drug without these limitations.

Now, the use of mechanical revascularization, of course, has been very important and has improved the treatment of angina. What isn't generally recognized is that many patients who have had successful PCI still continue to experience angina. The data shown on this slide come from the NHLBI Registry published about a year ago. They show the frequency of angina a year following PCI in several groups of patients, those with or without a previous myocardial infarction, those with and without previous coronary bypass grafts, those with and without previous PCI, and angina was persistent in all of these groups.

The bottom line is that among patients who underwent successful PCI the overall prevalence of angina was still 26 percent. Now, the ARTS trial was

an important trial which compared complete revascularization by means of coronary bypass grafting and PCI by stenting. Twelve months after intervention, there was still a large number of patients with angina. Seventy-nine percent of those in the stenting group were free of angina, which means that 21 percent still experienced it.

The surgical patients did better, but even 10 percent of those had angina. Now, even among the surgical patients, only 41 percent did not require anti-anginal medications. The bottom line in this trial, in which successful revascularization was carried out, 60 to 80 percent of patients were still taking anti-anginal medications and despite revascularization and pharmacological therapy, 10 to 20 percent of patients still experienced angina.

The impact of angina on the quality of life has been studied extensively. I'll give just two brief examples. A self-rating of health for angina patients showed that physical function, body pain, vitality and general health were all markedly diminished in patients with angina. Depression is a

very serious problem in patients with angina and, from this study, you can see that the percent of patients who were depressed rose as the frequency of angina pectoris increased.

So angina continues in many patients despite medical and mechanical intervention. The personal burden can deprive patients of their independence, forcing them to downsize their lives, leave employment or take reduced employment. The economic toll, therefore, is huge and it is important to develop new methods of therapy. When angina cannot be eliminated by current drugs, we should remember that it is typically due to their additive effects on blood pressure, heart rate and AV conduction.

There are other important side effects that we shouldn't forget: depression, fatigue, sexual and sleep disorders, which preclude complete relief and new therapies are needed to help fill the large void. So angina is a growing problem in the United States. It has been estimated that there were about a million people with angina at the beginning of the 20th Century, and that we now, as we've heard from the

American Heart Association data, have about 6.5 million Americans with angina, and the prevalence is rising and is expected to continue to rise as the population ages, as the epidemic of diabetes increases and as the number of patients surviving acute myocardial infarction increases.

It is interesting on this last slide to look back on the history of the treatment of angina. There actually have been only five really important therapies for angina in 125 years. Nitrates were introduced by Lauder Brunton in the 1880s. Beta blockers came along in the 1960s, calcium antagonists in the late 1960s, coronary bypass grafting in a major way in 1969, calcium channel antagonists in 1975, percutaneous coronary intervention in 1977.

Now, the presumed mechanisms of action of these classic treatments for angina are shown below. For the first five of these, the balance between oxygen supply and demand tends to be restored. And here as we're entering 2004, you're being asked to consider a novel compound whose principal mechanism of action appears to be metabolic. And it is notable

that ranolazine can be added to any, or any combination, of these earlier therapies.

I believe that you will find the experience with ranolazine, which is about to be presented, that this experience will open a new and significant chapter in the treatment of the condition described by Heberden. Thank you.

CHAIRMAN BORER: Thank you very much, Dr. Braunwald. Are there any questions or comments? If not, thank you very much.

DR. WOLFF: Well, thank you, Dr. Borer. I am Dr. Andrew Wolff from CV Therapeutics, and I will now discuss the efficacy and safety of Ranexa in the treatment of chronic angina. As we will see, the anti-anginal and the anti-ischemic effects of ranolazine have been demonstrated in five double-blind, randomized, placebo-controlled studies. They are related both to the dose of the drug and the resulting plasma concentration, as we have demonstrated across a broadly representative population of patients with chronic angina due to severe coronary artery disease.

The anti-anginal effects don't depend upon decreases in blood pressure or heart rate and in one study they were demonstrated to be as large or larger than those of atenolol at 100 milligrams once a day. In another study that we will review, the anti-anginal and anti-ischemic effects of the drug were demonstrated in patients receiving treatment with either atenolol or diltiazem at doses of those drugs that were felt to be optimal by their treating physicians.

The five studies demonstrating the efficacy of ranolazine included two pivotal Phase 3 studies performed with the sustained-release or SR formulation intended for marketing. One of these two trials, MARISA, evaluated patients withdrawn from beta blockers, calcium channel blockers and long-acting nitrates, that is, MARISA was the study of ranolazine as anti-anginal monotherapy.

The second and larger pivotal trial CARISA studied ranolazine in patients who are also receiving treatment with a standard dose of a beta blocker or a calcium channel blocker. Together, these two studies

enrolled over 1,000 patients. In addition to the two pivotal trials, three other studies enrolled 500 further patients with chronic angina and used in an earlier immediate-release or IR formulation. Now, these three immediate-release studies provide further support for the anti-anginal and anti-ischemic effects of the drug, as we'll see.

Together, MARISA and CARISA enrolled a broadly representative population of chronic angina patients. About three quarters of the patients were men. Over half were over the age of 65 and over 10 percent were over 75 years old. The concomitant illnesses that commonly occur with chronic angina were well-represented. About a quarter of the patients had diabetes and about a quarter had heart failure, two-thirds had a history of hypertension, more than half have had a prior myocardial infarction and about a third of our study population had undergone some type of myocardial revascularization procedure.

The patients randomized into MARISA and CARISA all had severe coronary artery disease based on their Duke treadmill exercise score. The Duke score

is an index of coronary disease severity with prognostic significance and it is calculated from the exercise duration, the degree of ST-segment depression and the presence and severity of exercise-induced angina during exercise testing. The entry criteria for MARISA and CARISA stipulated a Duke score at maximum of -10 at randomization. Current guidelines jointly issued by the American Heart Association and the American College of Cardiology classify patients with a Duke score more negative than -10 as high risk with an annual mortality of approximately 5 percent. And as you can see here, the average Duke score in our population was about -14.

I will now turn briefly to the MARISA study, a monotherapy assessment of ranolazine in stable angina. In MARISA, 191 patients withdrawn from other anti-anginal drugs were randomized into a four-period, crossover design study, in which patients received a week of treatment with each of these three active therapies, as well as placebo, in random order in a double-blind, double-dummy fashion for a total of three weeks of treatment with active ranolazine.

Patients would come to the clinic in the morning, 12 hours after their prior dose, the evening before that is at the time of trough plasma levels.

Following that exercise test, patients would take the final morning dose from that treatment regimen and then four hours later at the approximate time of peak plasma levels, they would have another exercise test. Here are the treadmill efficacy data for MARISA. Compared to placebo, each of the three ranolazine regimen studied caused statistically significant increases in each of the three major treadmill exercise parameters, exercise duration, time to angina and time to ST-segment depression.

These effects were clearly dose-dependent and were greater at peak than at trough. Most importantly, the primary endpoint of exercise duration at trough was met with increases with respect to placebo of 24, 34 and 46 seconds. The effects on the two secondary exercise end points, the time to ST-segment depression and time to angina, were actually all greater, 45 seconds or more.

The second pivotal study was CARISA, a

Combination Assessment of Ranolazine and Stable Angina. We intended for CARISA to be an assessment of the drug in a "real-world" clinical practice setting with each patient receiving one of these three background therapies at the stipulated doses which were chosen because they are the most commonly prescribed anti-anginal drugs in the world at their most commonly prescribed doses.

CARISA randomized 823 chronic angina patients into 12 weeks' treatment with ranolazine at doses of either 750 or 1000 milligrams twice daily or matching placebo and the randomization was stratified over these three background therapies. In this parallel group study then patients underwent exercise testing at trough, again, 12 hours after their prior dose, after two, six and 12 weeks of treatment and also had exercise tests at peak after two and 12 weeks of treatment.

Once again, each of the three major treadmill exercise parameters was improved by ranolazine versus placebo and, in particular, once again, the primary end point of exercise duration at

trough was met. In addition to treadmill exercise performance, angina frequency in nitroglycerin consumption were also assessed in CARISA. And you can see here that ranolazine reduced both angina frequency and nitroglycerin consumption to a statistically significant degree and in a dose-related fashion.

In both MARISA and CARISA, the ranolazine dose predicted the plasma concentration. The relationship between dose and plasma concentration was generally linear and is shown here. Now, as the dose predicts the plasma concentration, in turn, so does the plasma concentration predict the response. A large population based analysis of the concentration-response relationship for exercise duration included data from four different clinical trials. MARISA and CARISA, which I have just discussed briefly, and two earlier studies done with the immediate-release formulation.

This analysis included data on nearly 1,400 patients and nearly 11,000 pairs of exercise tests and plasma concentration data points. In this analysis, age, weight, race, congestive heart failure

class, diabetes and the presence, absence or type of background anti-anginal therapy each had no influence upon the slope of the relationship between the ranolazine plasma concentration and the increase in exercise duration.

This analysis thus indicates that the data from MARISA and CARISA obtained respectively with ranolazine is monotherapy or ranolazine in combination with the beta blocker are consistent with one another. The population analysis also showed a difference between men and women, with women having a somewhat lower slope for the relationship between plasma concentration and exercise duration. Ranolazine is an effective anti-anginal in women. Exercise duration in women increases with plasma concentration and, as indicated by the 95 percent confidence intervals around the slope, this is a statistically significant non-zero slope.

So women do, indeed, respond to ranolazine with increases in their exercise performance. The increase they experience is somewhat less than what we observed for men, but this is also true for many other

types of anti-anginal therapies, including drugs, bypass surgery and percutaneous intervention. But this doesn't necessarily mean that the response of women in the treatment of angina with ranolazine or these other drugs is actually less. It may be that exercise testing is not as fine a tool for the detection of therapeutic response in women.

And consistent with that possibility, is the fact that angina frequency and nitroglycerin consumption were decreased similarly by the two doses of ranolazine in both men and women. Thus, ranolazine does appear to be an effective anti-anginal in women, increasing exercise performance and decreasing angina frequency and nitroglycerin use.

Ranolazine was studied in a broadly representative group of chronic angina patients and we specifically examined those types of patients who might be more difficult to treat with some of the current anti-anginal medications, because of their depressive effects on hemodynamic parameters as described earlier by Dr. Braunwald. For example, this slide illustrates the subgroup analysis focused on

patients with systolic blood pressures less than 100 millimeters of mercury, heart rate slower than 60 beats per minute or PR intervals longer than 200 milliseconds.

You can see that in the CARISA trial this actually included about a third of the patients randomized. These p-values given here represent the treatment by subgroup interaction. In these analyses, a statistically significant p-value would indicate a major significant difference between the effect of ranolazine in the subgroup of interest and the effect in the other patients. But none of these p-values are close to statistically significant, which indicates that there is no major difference in the response to ranolazine between those patients with borderline hemodynamics and the others.

Now, these patients with low blood pressures and slow heart rates and long PR intervals could be viewed as resistant or possibly resistant to current anti-anginal drugs, because they are all having angina and exercise-induced angina and ischemia at a very low work load in the presence of at least

one hemodynamic parameter that could give pause before the initiation or upward titration of the hemodynamically acting drug.

In addition to the analyses in patients with borderline hemodynamics, we performed analogous subgroup analyses focused on other groups of patients not likely to tolerate the hemodynamic or other effects of current anti-anginal drugs. Patients with reactive airway disease, patients with congestive heart failure and patients with diabetes. In each of these analyses, the effect of ranolazine in the subgroup of interest was consistent with the effect demonstrated throughout the broad population.

Now, to put the magnitude of ranolazine's efficacy into perspective and to compare the anti-anginal pharmacodynamic profile of ranolazine to that of the hemodynamically acting agent, we'll turn to one of the Phase 2 Immediate-Release Studies RAN080. Chronic angina patients were identified using entry criteria that were essentially identical to those used to enroll MARISA and CARISA, and they were randomized then into a three-period, crossover design in which

they received a week of treatment with placebo, a week of treatment with immediate-release ranolazine at a dose of 400 milligrams three times daily and a week of treatment with atenolol at 100 milligrams once a day, a good dose of atenolol and, of course, in a randomized, double-blind, placebo-controlled fashion.

The ranolazine dose chosen at the time of exercise testing produced a plasma concentration of approximately 1700 nanograms per mL, which is right in the middle of the range of what is produced during dosing with sustained-release preparation at 750 milligrams three times daily. So it's a relevant dose for consideration. Here then are the treadmill exercise data from RAN080, and you can see both ranolazine, in these cream colored bars in the middle, and atenolol in the bright green bars on the end, both produced statistically significant increases in the three major treadmill exercise parameters.

Now, ranolazine and atenolol both produced similar improvements in time to angina and time to ST depression. But in this trial, the effective ranolazine was significantly greater than that of 100

milligrams of atenolol. Thus, in this study, the efficacy of ranolazine was at least as good as that of atenolol at 100 milligrams a day. More importantly, perhaps, however, was the way in which this effect was achieved.

The pharmacodynamic profile associated with ranolazine's improvement in exercise performance was very different from that of atenolol. Here are the data on rate-pressure product. As would be expected, atenolol decreases rate-pressure product at rest and even more dramatically at the end of exercise. In contrast to those effects of atenolol, ranolazine had no effect on rate-pressure product at rest, and was associated with a small but statistically significant increase in the rate-pressure product at the end of exercise.

So these patients' hearts then were able to do more mechanical work for a longer period of time before the symptoms and electrocardiographic evidence of myocardial ischaemia supervened. And this is consistent then with an improvement in the efficiency of myocardial oxygen utilization.

In another Phase 2 study, immediate-release ranolazine was studied in patients treated with atenolol or diltiazem at doses of those drugs considered to be optimal by their physicians. Patients received a single dose of immediate-release ranolazine or matching placebo on alternate study days in a two-period, crossover design. Exercise testing was done at 2.5 to 3 hours after dosing with these drugs, and so consequently it's important to realize that background therapies for themselves were also at their peak effects.

The 240 milligram immediate-release dose was studied in 25 patients, 15 of whom were on atenolol, 12 receiving a dose of 100 milligrams a day and 10 on diltiazem and again these were considered to be doses optimized by their physicians. As seen here, the 240 milligram immediate-release single dose, which produced plasma concentrations equivalent to those generated by 500 milligrams twice daily at trough, produced statistically significant and clinically meaningful improvements in each of the three major treadmill exercise parameters when studied over

background treatments of optimal doses of atenolol or diltiazem at the time of the peak effects of those drugs.

In summary then, with respect to efficacy, we've demonstrated the anti-anginal and anti-ischaemic effects of ranolazine to be both dose- and concentration-dependent. The effects are consistent throughout a broad population of chronic angina patients and don't depend upon decreases in blood pressure or heart rate. They've been demonstrated in one trial to be at least as great as those of atenolol at 100 milligrams once a day and in another trial they have been demonstrated over background treatment with optimal doses of atenolol or diltiazem.

I will now turn to the safety of ranolazine in chronic angina. In overview, shall I go ahead, Mr. Chairman?

CHAIRMAN BORER: Yes. Just a moment, Dr. Wolff, I think there are some clarification issues here. Paul?

MEMBER ARMSTRONG: Could we see CE-7 slide, please? I just want to go between CE-7 and CE-

9 to get a little better understanding. In this instance, the efficacy data shows -- I'm just trying to get a proportionate change, because the next slide is plotted somewhat differently. This is about a what, about a 5 to a 7 percent increase in the left panel over the baseline? Would that be about right?

DR. WOLFF: The increases on the primary endpoint are 24, 34 and 46 seconds. And with respect to placebo, yes, I mean, it's in that range.

MEMBER ARMSTRONG: That ballpark. Okay. And then if you go forward to CE-9, please? Now, in this instance, the plod is a change from baseline. I wasn't clear. So the presentation of the data is different here than it is in the previous slide.

DR. WOLFF: It is. The two studies are different.

MEMBER ARMSTRONG: Sure.

DR. WOLFF: I mean, because MARISA is crossover.

MEMBER ARMSTRONG: So just in terms of the baseline that we're talking about, what kind of baseline exercise performance would we be talking

about here? Just so I can get a sense of going back and forth.

DR. WOLFF: Yes. Well, I'm going to ask my statistical colleague, Dr. Mike Crager to give the numbers there.

DR. CRAGER: Mike Crager, CVT Biostatistics. The baseline is about 416 seconds.

MEMBER ARMSTRONG: Okay. And as I understand it, patients would have received either amlodipine or, I'm sorry, is it diltiazem?

DR. WOLFF: Amlodipine, diltiazem or atenolol. One of the three.

MEMBER ARMSTRONG: So how do we tell which is which?

DR. WOLFF: Well, these are the data for all the background therapies combined.

MEMBER ARMSTRONG: I understand that.

DR. WOLFF: Right.

MEMBER ARMSTRONG: So what I'm trying to understand is whether it makes a difference as to which background was chosen relative to what change you see. How much heterogeneity versus homogeneity

just so I could understand.

DR. WOLFF: Sure. We did do a similar analysis to one of the others I described earlier where we looked at the treatment by background therapy interaction, and we saw no statistical significance there. Here, in fact, you can see the data plotted. And, of course, when you slice and dice the data you will get some variability. But the treatment by background interaction statistic is 0.63, which indicates that there is no significant difference in the effect of ranolazine across the three background strata.

MEMBER ARMSTRONG: And when was the background therapy given relative to -- I wasn't clear in terms of it --

DR. WOLFF: They were given at the same time as ranolazine in the morning. They were all once daily, so they were given in the morning with the ranolazine.

MEMBER ARMSTRONG: Thank you.

CHAIRMAN BORER: Before you leave that CE-7 slide, and before we get to our Committee reviewer's

questions, can you go back to that CE-7? This was a crossover design, this study?

DR. WOLFF: Yes.

CHAIRMAN BORER: And in order for me to understand the effect of the drug relative to placebo, it would be easiest to make a determination after the first interval. Do you have the data to show us the relation of the effect of the drug to placebo after the first interval? I understand that we're dealing with a quarter as many patients there or a third as many patients, but I would like to see that if I can, so that we can avoid issues of carryover effect.

DR. WOLFF: I think we're putting up the slide with the first period analysis. Here, this shows the data by periods and we'll have Dr. Michael Crager come to the podium again to describe what we have done to exclude a carryover effect in the MARISA Study.

DR. CRAGER: So this slide shows the treatment effects by period. As you can see, the treatment appears to be closer together in the first period. However, if you look at the error bars around

the treatment means you can see that there is a lot of variability in the data. And if we put confidence intervals around those points, they would be twice as wide as the error bars.

When you look at a test for whether the treatment effects differ by period, the p-value for that test is 0.57. That indicates that any apparent differences between the effects of the treatment and the different periods is well within the limits of chance variability. So the most appropriate analysis to look at all of the data from the entire study, which is the results that Dr. Wolff presented earlier.

DR. TEMPLE: But it does seem to show a training effect, doesn't it? I mean, everything is getting better as the study keeps going.

DR. WOLFF: There is a training effect, yes, and I think that is typical for angina studies, but they all improve and the improvements are roughly parallel across the treatment groups.

CHAIRMAN BORER: Ed?

DR. PRITCHETT: What did you do with patients who didn't complete the study, who dropped

out without getting all the crossovers? How did you handle dropouts?

DR. WOLFF: The primary analysis was specified to be an analysis of what we call the all or near completers. And so it was data from patients who completed at least three of the four. And if that -- this was prospective identified -- population was greater than 75 percent of the enrollment, then that was going to be the primary analysis. In fact, it was over 90 percent of the patients. They had over three of the four periods end, and the great majority of them had all four periods. Then in order to try to analyze all the data, including those from patients that had even fewer than three periods, there was an analysis which Dr. Crager could describe, if necessary, using a generalized estimating equation which allows incomplete patients to be analyzed in a crossover design method.

DR. PRITCHETT: That's not necessary.

DR. WOLFF: Okay.

CHAIRMAN BORER: Blase?

DR. WOLFF: And they were very similar.

The GEE methodology and the primary analysis showed very similar results.

MEMBER CARABELLO: One of the natural niches for the drug would be for patients who are already optimally treated for their angina. And usually that requires several agents, at least most of my patients are on several agents. Further, that would test the hypothesis that this is adding a new mechanism of ischemia relief. Do you have experience with the use of the drug in patients who are already maximally treated with other agents?

DR. WOLFF: We don't have double-blind, randomized, placebo-controlled efficacy data. We do have patients that are receiving one, two, three other anti-anginal drugs in the Long-Term Open-Label Studies which have been ongoing in which patients have continued some of them for well over two years, and they do seem to be doing well, but we can't speak from controlled experience in that kind of patient population.

MEMBER CARABELLO: Thank you.

CHAIRMAN BORER: Bob?

DR. TEMPLE: You showed a study, I guess, with an IR form that suggested an increase in rate-pressure product, something that on the whole no other anti-anginal -- well, CCBs and beta blockers can't achieve that anyway. But we've discussed this previously, so I know what you said last time, but you may have looked further. The later studies, though, with the controlled release product have not shown an increase in rate-pressure product or maximum oxygen utilization or anything like that, right?

DR. WOLFF: Not a statistically significant one. At 500 milligrams twice daily at peak, the rate-pressure product is higher than on placebo in MARISA, but it's not statistically significant. So if we could, do you want to pursue this a bit more?

DR. TEMPLE: Well, it has something to do with whether there is a brand new mechanism here.

DR. WOLFF: Well, I think --

DR. TEMPLE: I don't know how persuasive people would find that.

DR. WOLFF: I would like to present the

data table, which shows the exercise performance data in relationship to the exercise rate-pressure product, as well as the heart rate and blood pressure, because I think this is instructive to how the drug is working. Okay. We have one that is a little less busy, but I can work from this one. Yes, this is good. Okay. Thank you.

Okay. So this is a crowded slide, but I think it walks us through the question that you are asking, Dr. Temple. Here you've got the standing and exercise heart rate and the systolic blood pressure on these two rows, and then their product, the rate-pressure product at the end of exercise for both MARISA and CARISA put together. Here is the 500 milligram dose for MARISA and then the 1000 and the 1500 from MARISA and then the 750 and 1000 milligram doses from CARISA are shown here in the blue box. And here are the data on exercise duration as a measure of exercise performance for each of those doses.

So in the first instance, you can see that there is really no effect at all on rate-pressure product at the 500 milligram twice daily dose, while

there was a statistically significant improvement in exercise duration. So this is the first piece of evidence that the effect of the drug can't depend upon any decrease in blood pressure or heart rate, because there really aren't any here.

Now, in the CARISA Study, as you mentioned, we do begin to see some slight decreases in rate-pressure product that do achieve statistical significance. However, again, you can tell that they can't entirely explain the effect of the drug on exercise performance for the following reason, and that is that, for example, here on 750 milligrams the exercise performance effect of the drug is greater at peak than it is at trough. But the slight decline in rate-pressure product is greater at trough than it is at peak. And it's similarly true for 1000 milligrams as well.

So while there are some small decreases in rate-pressure product that we did observe in the later clinical trials, they can't explain the effect of the drug to improve exercise performance completely. It can't exclude that there may be some small

contribution from them, but they can't overall explain it. And then finally, just observationally, these effects are much smaller than those of hemodynamically acting drugs. And in the RAN080 Study, I showed you the rate-pressure product on atenolol was down by several thousands of units, rather than just a few hundred.

DR. TEMPLE: Jeff, can I follow that up? I know beta blockers leave you with a lower rate-pressure product, because they lower the heart rate so much. But the point was to show an increased rate-pressure product at maximal exercise to show that somehow oxygen utilization or some aspect of the heart's work is improved. And having it go down only slightly, doesn't make that case.

DR. WOLFF: I think the best I can say is that in one study it does go up. It goes up significantly and it goes up in a patient population similar to what we observed in the other two. And in another study it doesn't go down at all, at a very similar dose and concentration. As you get the higher doses, as I say, I can't exclude that there may be

some additional contribution, but I think it is clear from the discussion we just had that the decreases can't fundamentally explain what is happening. There has to be some other contribution.

DR. TEMPLE: I guess I don't understand that. My impression is that calcium channel blockers leave rate-pressure product more or less unchanged. The idea being that somehow heart rate and exercise at peak are decreased enough so that you can exercise more before you reach whatever the critical level is, and that seems to be the same here.

DR. WOLFF: Well, these data go a little further. Here you can see the data from the CARISA Study at the time of peak plasma levels at the end of the study. The rate-pressure product is very close to the placebo line on drug, but one of the points that is consistent with what you are saying is that on the 1000 milligram group, some patients went from Stage 3 to Stage 4. Now, they didn't all do that. But it is interesting to note that none of them did it on the lower dose or on placebo.

So some patients actually did get to a

higher overall work load than on placebo. But yes, some patients stopped in here as well, and so the overall effect was not to have an average increase in rate-pressure product. But where it did occur, it occurred on ranolazine and only on the higher dose.

DR. TEMPLE: Okay.

CHAIRMAN BORER: Tom?

MEMBER PICKERING: Were any of these patients on long-acting nitrates? And do you have any data on long-acting nitrates?

DR. WOLFF: We didn't study long-acting nitrates, again, as a background treatment in either of the two pivotal studies. There are a few patients that were receiving long-acting nitrates in the earlier immediate-release studies. We didn't choose long-acting nitrates for background therapy for MARISA or CARISA, because at the time of trough plasma levels, that effect would have to be at zero if they are dosed properly, so, you know, they only work during part of the day. We do have a number of patients that have then gone on into open-label therapy and have been treated with long-acting

nitrates, and so there is open-label safety data with those patients.

CHAIRMAN BORER: Alan and then Blase.

MEMBER HIRSCH: I have three questions. First, regarding the unmet clinical need. You know, the study designs are helpful if they really inform us how a product might be used in the "real-world." So my question is, because I actually don't know the answer, like Blase, what fraction of American angina patients take one, two and three anti-anginal medications currently?

DR. WOLFF: Do we have a slide that shows that? We do have a slide that shows the fraction of patients dosed with the doses of drugs that were used in CARISA, but that's not directly to your question. That shows that the great majority of patients taking those drugs are on the doses that we used.

MEMBER HIRSCH: Right.

DR. WOLFF: If my memory serves me correctly, and I'm going only from memory, and I probably won't be able to show you data, but this comes from market research, I think it is somewhere on

the order of 5 to 10 percent of patients are taking three drugs. The majority in every study where we've ever looked at this take more than one. Most are taking two and some few are taking three. There's usually around 55 or 60 percent are taking two or three drugs.

MEMBER HIRSCH: The second question, if I could, regarding the dose-response. In the MARISA Study seeing that dose-response is somewhat reassuring, but many of us like to see a minimal effect or a no-impact effect of what might be received at something less than 500 twice daily. Have you defined that?

DR. WOLFF: We have from our population analysis where we've got an awful lot of plasma concentration data that covers the range, essentially, down to zero. And the analysis looks as though there is a zero intercept to the relationship between exercise duration and plasma concentration. So it just continues to go down linearly at lower and lower concentrations.

And so you could then predict that if we

studied -- well, if we got a 24-second improvement at trough in exercise duration on 500, then at 375 it would be on the order of about 18 seconds, and at 250 it would be on the order of about 12 seconds. And I think then the question becomes where is your judgment about a clinically relevant increase? But it does appear to be related to concentration really down to zero.

MEMBER HIRSCH: I hear that, but again is there clinical exercise that you can show us that's something less than 500 twice daily?

DR. WOLFF: We have an abundance of data with the immediate-release formulation that produced plasma concentrations below those that we now generate with the sustained-release, and those studies weren't effective. Here is one study that actually does give you some information there. This was one of the immediate-release studies in which three different regimens of ranolazine were studied at both peak, which was an hour after dosing, and trough, which was eight hours after dosing for two of the three times daily regimen, and it was done 12 hours after dosing

for a twice daily regimen.

And what you can see if you look through is that at peak, there were generally significant increases in treadmill exercise performance and there weren't any at trough. And in this study, the lowest plasma concentration that was associated with efficacy was on the order of around 1300. The highest plasma concentration at trough was around 500. So putting the totality of the data together, it looks as though if you were to speak of a threshold, it would be at around 800 nanograms per mL, which is what we get about at trough with 500 milligrams twice a day.

But it really isn't a threshold when you model all the data, because there is really a linear function there. But it is where we begin to demonstrate statistically significant efficacy in the usual range that people want to see of 20 seconds, 30 seconds.

MEMBER HIRSCH: One more potentially challenging follow-up, which is mechanism. I realize for many medications we don't really ultimately know how pharmacokinetics translates to clinical impact,

but what we're thinking of here is obviously something quite novel in that we're disassociating with the heart rate and blood pressure impact. So my question is how do we know this has a cardiac effect at all?

DR. WOLFF: I think we know it's a cardiac effect, because there were significant improvements in time to ST-segment depression in all of the studies. So, I think, I get your drift. There could be effects on skeletal muscle as well, and we do have preclinical data in skeletal muscle and the same kinds of metabolic shifts were seen. We know there has to be an improvement in myocardial performance because of the data on ST-segment depression.

MEMBER HIRSCH: So when this medication is given to healthy animals or normal volunteers, is there any change in exercise performance?

DR. WOLFF: We haven't done that in normal volunteers. We've done it in investigating heart failure in normal dogs, and in normal dogs we don't see any effect. And then after heart failure is induced in the animals, we do see then interesting improvements in left ventricular systolic performance

that occur without increases in heart rate, without increases in blood pressure or decreases and really do appear to be a central myocardial effect, because oxygen consumption actually trends slightly downward in those animals. But normal dogs we see nothing at the same dose.

CHAIRMAN BORER: Blase?

MEMBER CARABELLO: I had the same question. That last question was already answered. Thank you.

CHAIRMAN BORER: Before we go on to a different set of questions, we have Bob and Beverly and then we'll go on to Steve's list. The issue of extrapolating from the short-acting preparation or the long-acting preparation in part depends on our accepting the relation between effect and plasma level which, you know, at first glance might be reasonable, but it may not be.

And with that in mind, on your slide CE-9 on which you commented in your briefing book as well, it seems as if the effects are greater at trough, at least the absolute effect is greater at trough, the

absolute exercise time is greater at trough than at peak. The differences between placebo and active drug seem to be greater at peak than at trough. But the exercise times on placebo, the change from baseline on placebo is less at peak than at trough. This is an unusual set of data. It's not necessarily inconsistent with the idea that peak plasma levels are most effective, but I wonder if you can comment on this apparent discrepancy?

DR. WOLFF: Certainly. What we're seeing here is the change from baseline in exercise performance. And so at baseline, in the morning when we did the baseline "troughs" -- they really weren't troughs yet, because we hadn't begun the study, but we did the baseline at trough in the morning -- the background therapies of the amlodipine, atenolol and diltiazem were also at trough. And then when we did the baseline times in the afternoon for the peak tests that were to follow, the effects of the atenolol and the diltiazem and the amlodipine were at their peak effect.

And so, consequently, the changes from

baseline in the afternoon were all, as you've noted, generally smaller than the changes from baseline in the morning, because there was potentially a background effect of the drug. But as you note, the differences from placebo are clearly greater at the time of peak plasma than at trough.

CHAIRMAN BORER: Bob and then Beverly and Steve.

DR. TEMPLE: Only one of your trials was more than one week duration, and we thought we saw some decline in effect over time. So I guess, I think, you should discuss the duration of trials, the crossover trial really exposed people to just one week of treatment per period, I guess.

DR. WOLFF: But there were three total weeks of ranolazine.

DR. TEMPLE: Right. But it really hadn't been analyzed in terms of duration there. Maybe you could do that. So I think you should comment on that. I have to tell the Committee we haven't seen anything quite like that before. Trials are usually longer and we are worried about duration, so why don't you

address that to the extent you can?

DR. WOLFF: Okay. Well, here are the data by week from CARISA and as Dr. Temple points out, the difference at 12 weeks is slightly smaller than the difference at two. But, in general, you again see the learning effect, as we discussed before, on placebo. But the two active treatments are shifted upward in the generally parallel direction. And again, the arrows of the measurement are sufficient that really this is consistent with a parallel and maintained effect.

We've already seen the slide then from the MARISA Study which showed the learning effect and the difference sort of being maintained over the four week duration of that study. And then the only other data that I can speak to that go to chronicity of effect again come from CARISA, but from the withdraw portion of the study, which we haven't discussed. But at the end of the CARISA trial, the patients were re-randomized to look for evidence of rebound increases in angina with abrupt withdrawal.

And so the patients that had been on

placebo all just remained on placebo. But the patients on the two active doses were randomized, so that half of them were abruptly withdrawn to placebo and the other half continued on their active dose in a double-blind fashion and then there was an exercise test that was done 48 hours after the final dose. And as you can see here now, the improvements in exercise tolerance in the patients who continued on treatment remain, but the exercise performance in the patients who were withdrawn declined back down to placebo levels.

They didn't go lower than on placebo, indicating no evidence for any rebound increases in angina or decreases in exercise performance with withdrawal. So to Dr. Temple's question, these people are still exercising longer and in the same range that we were seeing after two, six and 12 weeks of treatment.

CHAIRMAN BORER: Before you take that away, the withdraw period was 48 hours, but the time to study state plasma level is three days, according to the data you sent us. Why did you choose 48 hours

as your testing time when presumably there should be some drug remaining?

DR. WOLFF: Well, after the last dose then the intrinsic half-life that is appropriate is the intrinsic half-life of the drug, not the apparent half-life due to the formulation, which is longer. And so dosing with the SR takes about three days to get the steady state, but after the final dose you just have elimination kinetics, and so by 48 hours everything should be gone. And you can see that it was. And, in fact, also we measured plasma concentrations to demonstrate that and they were effectively zero.

CHAIRMAN BORER: Beverly?

MEMBER LORELL: I would like to return for a moment to Dr. Temple's discussion about a unique mechanism for this agent since it pertains to our consideration of potential benefit versus risk. In many animal studies, one can profoundly perturb the utilization of glucose versus fat as a substrate for ATP generation based on the ambient energy source. And I suspect that, as in traditional clinical

practice, most of these exercise tests were performed with minimal food intake prior to that. Is that correct?

DR. WOLFF: The exercise tests at trough were done fasting or after a light breakfast, but then we had to let the patients eat and so the effects at peak were actually done fed, and so you could use peak and trough as a surrogate, I suppose, for fed and fasted. And in the population analysis, the concentration-response at peak isn't different from the concentration-response at trough.

MEMBER LORELL: Did you ever formally, even in a small number of patients, examine whether the anti-anginal effect was modified by intake of standard dose of carbohydrates?

DR. WOLFF: No.

MEMBER LORELL: Okay. Thank you.

CHAIRMAN BORER: Okay. Steve?

MEMBER N0ISSEN: Okay. Now, obviously, I think everyone in the room knows that what we're really trying to do here is to balance risk and benefit, so it's an efficacy safety question. So I

want to probe with you just a little bit on the efficacy side. Although, I think, you know, the data you presented are reasonably compelling.

Could you put up slide CE-4? You know, we heard, I thought, a very nice presentation from Dr. Braunwald about the unmet need, and one of the points that was made is that patients are treated now maximally. I mean, everybody gets an angioplasty. I mean, it's like if you come to the Cleveland Clinic, you go home with an angioplasty. That's easy.

So I was just amazed at this slide, which showed that only a third of the patients in your control trials had had previous revascularization, and so the immediate question that came to mind was what countries was this done in? Did you do this in the third world where revascularization is less commonly available, because I really want to know for those patients that come to the Cleveland Clinic and get their beautifully performed angioplasty, but occasionally have angina thereafter, what's going to happen. And yet, very few of your patients had been revascularized.

DR. WOLFF: The study wasn't done, I don't think, in the third world, but it was done at some centers outside the United States from Central Europe and Eastern Europe, and it is true that the use of interventions in those countries is lower. But I think there are two pertinent points to the observation that you make. One of them is that we did do an analysis similar to one of the ones I described earlier, looking at patients who had been revascularized versus those who had not been revascularized, and there was no evidence for a major difference. The drug was effective in the patients following revascularization.

And then also pertinent was we did a similar analysis looking at the region to see if there was an effect of the region on the result and, again, the treatment by region interaction was not at all significant, suggesting that the effects were generally similar across the different regions in which the trial was performed.

MEMBER NISSEN: But again, relating to the unmet need, if the problem is in the U.S. that despite

revascularization, we need better and more anti-anginal agents, it would seem to me that you want to try to make that case. And you know, the other problem is what is the power here? I mean, if you ask the question about differences in revascularization versus no revascularization, you know, you're now talking of the 1,000 or so patients, really only about 300 or so of them have actually had revascularization.

DR. WOLFF: The differences are not large and here is one of the examples, and we have done this for MARISA and for CARISA at peak and at trough. So I mean, we could actually run through all four of those slides, so you could get an impression of the totality of the data. Here you see CARISA at trough. The treatment by subgroup interaction, p-value is 0.22, and the effects are generally similar.

I think it would be instructive to look at CARISA at peak and the MARISA at peak and trough for the patients who have been and who have not been revascularized if we could get those other three slides up. Yes, great.

Here it is at peak in CARISA and again,

you know, you can see that the treatment by subgroup interaction statistic is far from statistically significant. The blue bars are bigger than the placebo blue bar or the red bar is bigger than the placebo red bar. In MARISA we see very, very similar results across the three treatments, whether the patients are revascularized or not. And again, a very high p-value for the treatment by subgroup interaction.

And then exercise duration at peak, again, treatment by subgroup interaction, the p-value is very high. The balance of patients in the revascularized versus not revascularized group is pretty reasonable, so I think it's concludable that the drug works whether or not patients have been revascularized.

MEMBER NISSEN: Okay. Thank you for that. Now, I would like to see CE-7. The maximum dose that you are recommending that be approved is what?

DR. WOLFF: Is 1000 milligrams twice a day.

MEMBER NISSEN: So would you suggest then that we ignore the efficacy data for 1500 milligrams

bid, because we're not going to be considering that?

DR. WOLFF: I think they are instructive in understanding the drug and its properties, but I think when we review the adverse event data, you will see that the increase in adverse events from 1000 to 1500 is probably disproportionate to the more linear increase in efficacy, and so it's more for the tolerability reasons that we recommend against higher doses than 1000.

MEMBER NISSEN: Yes. I really wanted to bring this up just to point out to the other members of the Committee that we're looking at data here for doses that are beyond the range at which we're going to consider. So I just think we have to keep that in mind as we look at this.

And now, let's see CE-8. I find CARISA much harder to analyze than MARISA and let me see if I can tell you some of the problems that I have and see if you can help me with them. One is that there is a drug-drug interaction going on here. I think we know from the PK data that diltiazem substantially elevates the serum levels of ranolazine, and so those patients

that are in the arm that get diltiazem, you would expect, and I presume that they did have higher serum levels than those that got amlodipine or atenolol.

DR. WOLFF: They did. They are about 30 or 40 percent higher.

MEMBER NISSEN: Okay.

DR. WOLFF: Which is what we expected and why we designed the study this way.

MEMBER NISSEN: Right. Okay. And so that's an issue. The other issue is that atenolol, while it's given once a day for hypertension, has a half-life of about six hours. So now, the question is was this done? These measurements were made at both peak and trough? Is that correct?

DR. WOLFF: Correct.

MEMBER NISSEN: Yes. So did you see any difference in the effect at peak and trough in the atenolol arm related to the fact that you were at trough, the atenolol was no longer present or not to certainly a significant extent? Do you see the issue there?

DR. WOLFF: Yes.

MEMBER NISSEN: You have two drugs that are very long-acting, amlodipine and diltiazem you're comparing, and one drug is very short-acting, atenolol. And so I'm trying to understand what happens when you mix those drugs together.

DR. WOLFF: Well, here are the data at trough, and we should probably then show the data at peak, as well, for the three background therapies. And again, the treatment by background interaction statistic is not significantly different. So while you do see, for example, on the diltiazem, you know, maybe a more clearly dose related increase, still the effects are generally within the range of one another on the three backgrounds. And here is the slide with the data at peak, and you can see that the increase -- I don't believe we have a slide where I can put peak and trough right next to one another for you, but the increases actually are somewhat bigger in the atenolol stratum at peak than at trough.

MEMBER NISSEN: Yes. Go ahead.

UNIDENTIFIED SPEAKER: No, I'm okay.

MEMBER NISSEN: Okay. All right. Okay.

Again, it's really tough, because obviously when you have a drug-drug interaction, you have got more than one thing going on. You have got the question of added efficacy, but you also have the question of diltiazem elevating the serum levels. So I just want to make sure that I understand this.

DR. WOLFF: We did do an analysis where we reduced in theory the efficacy that would have come from the higher plasma levels in the diltiazem patients proportionally, and it really made very little difference to the overall outcome. Dr. Crager can describe that to you.

DR. CRAGER: So for this analysis, we used the linear relationship between plasma concentration and efficacy and put in the known elevation of diltiazem to ranolazine concentrations and here are the results. So from that, the first column of results there is the primary efficacy analysis. The second one is what you get when you adjust as though there were no plasma concentration elevation effect of diltiazem, and as you can see it doesn't make all that much difference.

MEMBER NISSEN: Okay. All right. That actually is very helpful. Thank you very much.

I'm still having a great deal of difficulty understanding why the apparent effects at trough are greater than peak in CARISA. Could you just explain to me what your hypothesis is for why that's happening?

DR. WOLFF: Sure. If we could, why don't we put up CE-9 again, because I think it's easier to look at that way. The CARISA efficacy data. So again, these are changes from baseline. And what I don't have presented here, but if it's worth looking at, maybe we could tee up a table that gives the baseline data for the CARISA trial. I do believe we have -- I think we have a data table with baseline on it. But the baseline in the morning is a good bit shorter. I think it's about 70 seconds shorter in the morning than in the afternoon.

Now, we don't have data comparing to placebo the effects of the background therapy. They were background and they were baseline. But the baseline in the afternoon was a good bit longer and

presumptively it's because the effects of the atenolol and the diltiazem and the amlodipine were about at their peak at four hours after they were given as well. And so --

MEMBER NISSEN: Well, no. That's not possible. I mean, amlodipine has a half-life of 50 hours and so you have steady, it's very much steady state. So at least on the amlodipine arm, that's very unlikely and diltiazem, you know, sustained-release is pretty much a zero-order kinetic model as well. So that doesn't make any sense, does it?

DR. WOLFF: Well, what the data were and for whatever reason --

MEMBER NISSEN: Yes.

DR. WOLFF: I won't hypothesize on the reason. The data are that the baseline exercise duration at the time of peak, so, you know, four hours after dosing, but in the absence of dosing with ranolazine, because it's at baseline, was a good bit longer. And so consequently, the changes from baseline, from that higher baseline, were smaller at peak, but the difference from placebo was bigger. So

that is why these changes from baseline are smaller at peak, but the drug effect, which is the difference between the colored bars and the gray bar, is bigger at peak than at trough.

CHAIRMAN BORER: It may be why. I mean, we don't really know why the change from morning to afternoon occurs, and the fact that it does occur doesn't a priori mean that the changes should be smaller on placebo or on drug just because the baseline was higher. I mean, we don't know that, but it doesn't matter. I mean, these are the data.

Before you on with the questions, Steve, Bob and Alan, I think, had some points to make.

MEMBER NISSEN: Sure, sure.

DR. TEMPLE: Just on the last point, that is why you have a placebo group, because we don't understand everything as well as we should. Placebos keep you from needing to. On the question of the ability of ranolazine to add to the effect of existing therapies, I just want to provide a little bit of context.

Ordinarily for a new angina drug, we don't

ask that it be better than anything else. We don't particularly ask that it show in the additive effect when you add it to other drugs. Although, that would be interesting to know. The reason that's relevant here is that we're trying to balance potential risks, as Steve said earlier. So these studies use very modest doses of the drugs. I don't remember the dose-response for diltiazem anymore, but I know amlodipine at 5 milligrams is sort of barely there as an anti-anginal. It doesn't work very well even if it's very popular. It doesn't produce much edema at that dose. And atenolol 50 once a day, you know, 12 hours later or something or 24 hours later is also barely there.

So in some sense, our worry about interpreting this is if you gave a person -- if you compared 10 milligrams of amlodipine with 5 milligrams of amlodipine, the 10 would look better, but that wouldn't exactly be an additive effect. That would be called getting to the right dose. So I guess the question here is, and I'm flushing this out, because it was one of the questions we raised, I want to give you an opportunity to answer it. We didn't think this

was very good evidence on whether a person on reasonably identified maximum doses of some or other drug could get an added benefit because of a different mechanism or whatever the reason might be.

I wondered if you wanted to address that, because one of the things we asked for in the letter was a study that really pinned this down. So I just think I would like to hear what you -- you need to present what you think about that.

DR. WOLFF: Okay. Well, we have looked already a couple of times at the background strata data for CARISA, and I would point out that at the time of peak plasma, well, at the time of peak exercise testing, and that's about four hours after dosing with the background treatment with atenolol, and so according to Tenormin labeling, the early effect of atenolol is maximal, not of that dose, but of the drug is maximal after doses of about 50 milligrams is what it says. And so one could then argue that showing efficacy at peak with ranolazine was efficacy under conditions of the maximal effect available from atenolol. So there are those data.

And then if we look at the data from 072 again and consider the doses of atenolol and diltiazem that were used then, the atenolol dose was 100 milligrams once a day, which I think people would agree is a fairly healthy dose. It was 50 in three patients. It was 100 in 12. And they were supposed to have been optimized, so we can only presume the patients that were on 50 couldn't tolerate a higher dose. We did demonstrate efficacy over that dose. And then diltiazem was administrated in that trial to those patients at 180 milligrams three times daily. I'm sorry, 60 milligrams three times daily, which is perhaps not sounding like a large dose, but it's interesting to consider the pharmacokinetics of diltiazem and when the exercise tests were done.

If you look at this slide here, it shows the plasma levels that would be predicted of diltiazem given as 60 milligrams three times daily as it was in Study 072. And exercise testing was then done in this interval right here, which interestingly is very analogous to the plasma concentration at trough with 300 milligrams a day. And if we do look at the

product labeling for various diltiazem formulations, the effect of diltiazem with the once daily dosing at trough is plateaued at around 300.

So I think these data do support that there is a drug effect that is measurable and clinically meaningful over the maximal effect of atenolol or diltiazem. Here are the data that I was just mentioning with respect to the effects of diltiazem. You can see that here, 360 milligrams from this product's label would appear to be a plateau. Here it's somewhere between 240 and 360. So at around 300 once daily of the once daily formulation of diltiazem, you're at something of a plateau effect, and these are the conditions under which those exercise data were obtained.

CHAIRMAN BORER: Steve?

MEMBER NISSEN: Yes. I think what Bob is probing, and I was also wanting to go there, as well, is that in judging the relative risk and benefit here, one of the things that would make a big difference, I think, at least to me, I'm not sure about other members of the Committee, is that if we knew that this

agent produced significant efficacy in those patients that were on maximally tolerated doses of anti-anginal agents or couldn't tolerate them, and these are refractory patients, patients that we can't help any other way, then that would be a very important mitigating factor, you know, against the potential safety concerns.

And so I'm looking for what evidence you can provide us with that people that I just can't treat, you know, in any other way can be benefitted by the agent in terms of significant prolongation of exercise time.

DR. WOLFF: Well, I think these data may go to that point most directly. These are the subgroup data looking at the effect on exercise duration in patients who have had systolic blood pressures less than 100, heart rate is less than 60 or a PR interval greater than 200 milliseconds. Now, in CARISA that particular parameter was over a background of amlodipine or diltiazem in many of the patients and -- I'm sorry, atenolol or diltiazem, amlodipine and the others.

And so, you know, one could argue that these patients with these vital signs wouldn't be receptive to higher doses of hemodynamically acting anti-anginal drugs. And yet, we see ranolazine did provide efficacy, generally speaking, in that subgroup that was comparable to the patients who had normal vital signs and AV nodal conduction.

We did similar analyses to these not just for exercise duration, but for time to angina, time to ST-segment depression and for angina consumption, I'm sorry, angina frequency and nitroglycerin consumption in CARISA and they all look like this. There is an effect that is very similar in the population with the borderline hemodynamics or AV nodal conduction to the patients without. So that indicates that you could expect to see efficacy in those folks that is about the same as in the general population we studied.

MEMBER NISSEN: That was half of my question though. The other half would be, you know, people that come in and they have adequate blood pressure and heart rate to tolerate maximal anti-anginals, and so you push their anti-anginals to

maximum including nitrates and they still have angina. So now, you add ranolazine and you find out if those patients that are on triple therapy can get -- I mean, it would be very powerful, persuasive to me as a cardiologist, to see data.

I was also troubled by the fact that there is nothing about nitrates in any of this database. I mean, why were nitrates just ignored here? It is certainly a very commonly used anti-anginal agent and they don't appear anywhere in the data.

DR. WOLFF: Well, they do appear insofar as nitroglycerin consumption was allowed, ad lib, in both the studies and it was measured in CARISA and we did see that there was a decrease in nitroglycerin consumption in CARISA. We didn't use long-acting nitrates as a background therapy because of the need to demonstrate efficacy at trough ranolazine levels as a primary endpoint. And because of the nitrate holiday that's necessary daily in order to maintain responsiveness to nitrates, at trough in the morning nitrates would have effectively been placebos. So it's true, we don't have double-blind, randomized,

placebo-controlled efficacy data over a background of nitrates.

But there is no pharmacological reason to expect that it wouldn't work, and we do then have patients who go on to open-label treatment and receive long-acting nitrates because, as you say, they are very commonly used, and we have seen no problem in co-administration of long-acting nitrates with ranolazine nor mechanistically with nitrates would we expect any.

MEMBER NISSEN: Right. No increase in syncope, for example?

DR. WOLFF: Well, we'll get to syncope later and I can address that issue.

MEMBER NISSEN: Yes, I want to come back to that, because one of the things I have got to know as a cardiologist, and the FDA has to know in writing a label, is to tell people how they might mix this into the therapeutic regimen the patients are on, and I must tell you most of my patients with medically significant refractory, particularly refractory angina, are going to be on long-acting nitrates. And I just don't have anything in your database that tells

me what to do with those patients.

CHAIRMAN BORER: Alan and then Tom.

MEMBER HIRSCH: Well, my question might extend a little bit of how we might use this medication in practice, so I want to explore the efficacy dose-response one more time. You know, in this database you have, I think, shown to me that there is a clear efficacy signal and a dose-response, but you have also stated that we tend to want to look at pushing the dose, so we get maximal symptom relief, because what the patient is looking for is symptom relief.

So what I want to ask is if this drug were applied in practice, I would tend to increase the dose until I achieve some net clinical benefit or a wall of adverse effects. Is there anything in the large database even with individual release or short-term usage that shows the dose-response of individuals up to peak efficacy or tolerance?

DR. WOLFF: I think the best data come from MARISA where it wasn't really a titration, per se, because the order of the doses was random, but you

do see very clearly there in a crossover design study where the doses are being applied repeatedly to the same individual, a clear dose-response, and you also will see when we get to the adverse events, I think, a clear dose relationship to the more clearly drug-related adverse events. And in our open-label experience, we do allow -- in fact, that's how they are designed. Patients start at 500 and they titrate to 750 and go to 1000. So we have that kind of experience with titration.

CHAIRMAN BORER: Tom?

MEMBER PICKERING: The issue here is not whether this agent prolongs survival. In fact, there are questions about whether it might have adverse effects, but whether it makes patients feel better. And I am having some difficulty interpreting what a 20-second prolongation of exercise time on a treadmill test means to a patient. You also said that the number of anginal attacks goes down from, I think, about 3.5 to 2.5 a week, but there is also side effects. Something like 5 or 10 percent experience nausea and dizziness.

And I wonder do you have any evaluations, particularly in CARISA, about overall quality of life and whether patients actually felt better while they were taking ranolazine as opposed to placebo?

DR. WOLFF: We don't have data specifically on a quality of life index. The angina frequency decrease was actually from more than about four attacks per week at baseline, and the decrease was a little fewer than two per week on a lower dose and a little more than two per week on the higher dose, which was greater than on placebo.

With respect to the -- if we could have the slide that was up there, please? With respect to the meaningfulness of 20 seconds, I would like in a moment to ask Dr. Peter Stone to comment on the magnitude of improvements in exercise performance with anti-anginal drugs, but I will make a few points first, which I think are sort of interesting.

And that is to recall that the improvement in exercise time comes at maximum exercise performance, which is a level of exercise that is not typical of the patient's day-to-day life. And so if

you take the increase in mets that occurs during that increased exercise time and imagine that it would be translated into stage zero exercise performance at the beginning of the exercise test, then the improvements that the patients would see at the lower work load are, in theory then, quite a bit longer.

And I think then the other instructive point is that improvements on the order of 20 or 30 seconds as we saw across our trials were at least as great as what we saw in the same patients in the Crossover Design Study with 100 milligrams once daily of atenolol, which I think, you know, we all have a feeling for in terms of its efficacy. But maybe, please, Dr. Stone could also address this topic.

DR. STONE: Thank you very much. Peter Stone from Brigham and Women's Hospital. It's interesting to point out that for decades of evaluation now, the standard improvement in the anti-anginal therapies is in the range of 25 to 35 seconds really across all forms of therapy. In addition, it's interesting and I think quite impressive that even despite combination regimens or coexistent therapies,

there is still an incremental 25 to 35 percent or 35-second increase in exercise duration.

And interestingly in a broader context, the recently reported RITA-2 Study from JACC a month or so ago noted that the difference between angioplasty associated improvement in exercise duration versus medicine is also 25 to 35 seconds. So really all of our therapies have been in that range of improvement. Thank you.

CHAIRMAN BORER: Bob?

DR. TEMPLE: Well, I would endorse that, too. In the old days, which nobody except perhaps Jeffrey will remember, we used to have people with enough angina attacks that you could actually see quite a nice improvement in the angina rate. They would have 10 a week or something and it would drop to three a week or something and that was good.

Nowadays, as you could see here, and actually there are more here than in a lot of trials we have seen, the main benefit of anti-anginal drugs is that you can exercise on a treadmill a little longer. You can spend 10 seconds, 20 seconds, 30

seconds more on a treadmill. But we have always believed, foolishly or not, that that corresponded to the kind of effect on angina episodes that you would see if you had a population that had angina episodes.

My recollection, this is old. Usually, people fail as the stage of the test is increased. So it's not two minutes or three minutes into a stage that you see the 40 millisecond difference. It's how long you can do when somebody increases the exercise burden and not surprisingly when you have done that, it's a fairly big change. They fail pretty rapidly. So a 20, 30-second increase is sort of what we have seen with all the drugs. That's what all of the approved drugs we're looking at have done also.

CHAIRMAN BORER: Doug?

DR. THROCKMORTON: Dr. Hirsch, I want to take you back to a comment you said. You said you think you have a good handle on dose. Did I misunderstand that, because one of the things that the Agency had looked at was the sort of numbers in the two pivotal studies and at least there was a suggestion. You know, if you look at the 3033, and

I'm sorry, Andy, I don't remember which name that one is.

DR. WOLFF: That was CARISA.

DR. THROCKMORTON: Thank you. Sorry.

DR. WOLFF: Sure.

DR. THROCKMORTON: 750 and 1000 are at 30 or sorry, 27 seconds and 26.8 seconds at the end of 12 weeks for effect, and 500 in the other study for what that's worth. It was roughly at the same number. And then 1000 and 1500 in the 3031, in the CARISA Study, were at 50 and 55. I'm not sure if those are different or not.

So help me understand how well you think you understand the dose, as opposed to concentration, because I think I would say, like Dr. Wolff, that the Agency believes there is a concentration effect relationship here that has been well-characterized. We don't disagree with that. It's the nature of the subject, intersubject variability, and the difficulties describing dose. So help me out here.

MEMBER HIRSCH: Well, I just want to be very precise. I feel some clarity that there is

efficacy in that 500 to 1000 twice daily signal. Let me first move up. I am less clear about, obviously, the dose-response moving upward to 1500 twice a day and I am uninformed moving below 500 twice a day. And I only raise this question now, so that later when we talk about safety, we can come back to that. Clear?

DR. THROCKMORTON: Okay. And so then you believe 1000 is more than 500?

MEMBER HIRSCH: Currently, yes.

DR. THROCKMORTON: Okay.

CHAIRMAN BORER: Before we go on to Steve's questions again, I want to go back to the issue of atenolol's background. First of all, I have to note yesterday I mentioned the 1982 aspirin hearing and Steve said he hadn't been born yet and now, you indicate quite correctly that I do remember the previous studies of anti-anginal drugs. And one of them --

DR. TEMPLE: It's okay, Jeffrey. The best years are ahead.

CHAIRMAN BORER: Right. One of them involved the development of bepridil and I'm raising

this issue because of what I think I heard was a standard because of the potential safety concerns. When bepridil was developed it did involve QT prolongation. It was an effect of anti-anginal drug and ultimately, it was approved for patients who were refractory to other treatment or who needed additional treatment after other treatment, who couldn't tolerate other treatment in a study of patients who could not tolerate diltiazem.

DR. TEMPLE: Didn't respond to diltiazem. They were then randomized back to bepridil versus diltiazem and bepridil won.

CHAIRMAN BORER: Right. That's the point though. It was one drug. And what I'm hearing here is the suggestion that unless you can show that you're better than a combination of all the drugs you can tolerate, you know, that we may have a concern in terms of benefit-to-risk relationship, and that may be right. I just point out that the last time this came up, that wasn't the standard we used and that ought to be considered as we think about standards now.

I would like to go back to the atenolol

slide, the background therapy slide that you showed. I'm not sure that I fully understood it and I don't want to overstate this issue, because, in fact, the numbers are relatively small and subgroup analyses weren't pre-specified, etcetera, etcetera. But can you put up the slide where you showed the effective placebo and of drug at two different doses on the different background therapies? Okay.

Now, as I look at that, this is a trough. Can you tell me if there is a difference between the effect of placebo on the background of atenolol and the effect of ranolazine 1000 milligrams twice a day on a background of placebo? I just can't --

DR. WOLFF: This is one of the smaller differences and it is as you say, when you begin to get into subgroup analysis, the variability in the data increase. And so it is true that at trough in CARISA, the improvement over placebo on atenolol actually was numerically bigger than the improvement at 1000. But again, in general, the effects of ranolazine were consistent across the three background strata as indicated by the treatment by subgroup

interaction, p-value of 0.63. So we'll always find these sorts of increased noisiness as you slice the data more and more.

CHAIRMAN BORER: Yes. I mean, that may well be the case. And show the peak, the peak effect, as well, please. There, too, is there a difference? Maybe it's the angle at which I'm looking.

DR. WOLFF: It's small.

CHAIRMAN BORER: And it wasn't in our briefing.

DR. WOLFF: It is small.

CHAIRMAN BORER: Yes.

DR. WOLFF: The 1000 milligram dose over the atenolol background in CARISA had numerically smaller effects at both peak and trough.

CHAIRMAN BORER: Okay. Steve, did you want to go on with your questions again?

MEMBER NISSEN: I just wanted to answer. I wanted to make sure that you understood. I wasn't trying to set a new standard here, but I wasn't really asking that ranolazine beat combination therapy. I was asking that it show some benefit in those patients

that were maximally treated, and it's a very different question.

DR. TEMPLE: Right. I think what bepridil was asked to do was very difficult, beat another member of the same class. I mean, you really don't expect it to be able to do that, but it did.

MEMBER NISSEN: Yes.

DR. TEMPLE: The thought we have had in the letter was you're asserting that this is a different mechanisms. Well, then it ought to add to things that have the same old mechanisms. So that's what we thought.

MEMBER NISSEN: And what I was trying to opine here is that if I could see very convincing evidence that on a background of maximal treatment, there was an incremental benefit, clinical benefit for patients, that would mitigate to some extent against the safety concerns, because it would make me believe that I was going to offer patients something I couldn't offer them any other way.

DR. TEMPLE: Yes. Well, that is certainly the thought we expressed in the letter.

MEMBER NISSEN: Yes.

DR. TEMPLE: There is a lot to discuss about.

MEMBER NISSEN: Yes, there are lots of --

DR. TEMPLE: It's necessary and all that.

MEMBER NISSEN: Yes, lots to discuss. Now, one last question and it's just a flyer here, but there would be potentially a way to look at mechanism and that would be to do PET scanning and look at F-18 deoxyglucose uptake. Has anybody proposed or even done a small study to look at fluorinated, you know, glucose as a way of detecting whether glucose utilization is actually going up? It should be very sensitive.

DR. WOLFF: That study has been proposed many times. It has not yet been done. We have one concern about, you know, measuring uptake instead of oxidation, but in animal studies where we have looked at glucose uptake and free fatty acid uptake, we have in several different models of the ischemia seen that ranolazine does tend to increase the glucose uptake and decrease the free fatty acid uptake. But the PET

Scan Study has just not been done yet.

CHAIRMAN BORER: Beverly?

MEMBER LORELL: In line with that question, you talked about the diabetic subgroup very briefly and I think for many of us on the Committee, this is a group of great interest since they can be, as alluded to in Dr. Braunwald's presentation, one of the more challenging groups to treat with available agents. On the other hand, if there is, in fact, a novel mechanism, one could think of some scenarios where the ability to use glucose as substrate might be in part limited by the physiology of diabetes itself.

Rather than showing that relationship between dose concentration and exercise time, which is your only comment about the diabetic in your presentation, do you have a bar graph for diabetics, for an exercise time?

DR. WOLFF: Here are the data from CARISA at trough and again, you know, we have four different graphs and if you found it instructive, we could look at all four of them. I think we should. So here are the data and the blue bar is the patients with

diabetes and the red bar is the patients without, and the treatment by background interaction statistic was .89, indicating again not a major difference between those with diabetes and those without.

Here are the data at peak. Again, you see the effect of the drug to increase exercise duration in both subgroups, and here are the data from MARISA at trough and then MARISA at peak. And I guess the other thing that's worth mentioning, it's in the CARISA study, because it was a parallel group study of 12 weeks duration, and we also measured the hemoglobin A1c in the diabetic patients and we found that it declines over the 12 weeks of treatment to a significant degree at about 1 percentage point in a more or less dose relation fashion.

So also, there were no untoward effects on lipid parameters neither in the general population nor in the diabetics. So it did appear to be a generally safe and equally effective drug in the diabetics and in those without diabetes.

MEMBER LORELL: Thank you.

CHAIRMAN BORER: Alan?

MEMBER HIRSCH: I was going to avoid subgroup discussions, but as long as we're getting there, let's slice and dice a bit. I want to talk about the subgroup of women. We spent a lot of time yesterday at the panel making sure that we clarified the efficacy in this, more than half of Americans who also have angina. And I know you have stated in the briefing booklet that you have looked for reasons why the change in exercise time for PK might be different.

But just to go on the record, is there anything else we can learn about the difference in efficacy in women? And I want to go back to use of anti-anginal medications. Now, something that Steve said, background use of PCI. What Bev said, even dietary fat intakes and, you know, what's eaten, something different about the population.

DR. WOLFF: What I can show you in addition to what we have already discussed, I mean, we have seen the slope is positive, but lower in women. The decline in angina and in nitroglycerine use is very similar between men and women. We can see that briefly again here. The other data that we have in

our database, that I think are instructive to your point, come from RAN080, which we discussed briefly.

And let me show those data divided between the men and the women. You will recall this was a three-period, crossover study in which patients received a week of treatment with placebo, a week of atenolol at 100 a day and a week of ranolazine, and you will recall that both ranolazine and atenolol were superior to placebo in improving treadmill exercise performance.

Here you see the data for men and women broken up with men in this column, women over here, and then here are the data for increase in exercise duration on atenolol compared to ranolazine. Now, in this particular study, the improvement in total exercise duration was very similar between men and women, not quite so similar for atenolol.

Interestingly, when you look at the other primary, not primary, but major exercise variables, again, we do see that women were afforded somewhat less of an increase on ranolazine compared to the men. But the difference on atenolol at a healthy dose, a

drug I think that we're all very familiar with and confident with, the difference was actually worse for the atenolol between men and women than it was for the ranolazine. So it suggests that this is something not about ranolazine, but about the differences that we're coming increasingly to appreciate between angina and coronary disease in men and in women.

CHAIRMAN BORER: To complete the sub-population issue, the analysis of sub-populations, you mentioned that there was equivalent effect across the various sub-populations you looked at based on race and age and what have you. Do you have a slide where you can just show us those numbers for non-Caucasian and age?

DR. WOLFF: Why don't we run through what we call the city plots and look at all of them, because I think you will see that the totality of the data is just generally instructive. Okay. So here we have the group that we focused on in the main presentation of the patients with the borderline vital signs or AV nodal conduction. Here are the patients with heart failure, diabetes, reactive airway disease

and then on the bottom we have represented the effect in patients that are in any one of these subgroups.

And again, although the bars are certainly not going to all be the same height, the effect is always in the same direction and generally similar at trough in CARISA throughout all the subgroups. Looking again at peak, we see again insignificant treatment by background interactions and probably more importantly, just examining the data, a generally similar effect in patients within the subgroup compared to those not in the subgroup.

Moving then on to the MARISA trial where we have the three different doses. Again, you see that there are no statistically significant treatment by background interactions, generally similar responses in the patients in the subgroup of interest compared to those not in the subgroup of interest.

And then at peak in MARISA, one of the few times where we actually did see a statistically significant treatment by background interaction was in the patients with heart failure in the MARISA trial. And here you can see that that was actually because

the patients with heart failure at peak had a statistically significantly greater improvement in their exercise performance on ranolazine than did the other patients.

DR. THROCKMORTON: Jeff, I think you asked about gender and age.

CHAIRMAN BORER: Right.

DR. THROCKMORTON: And race, those things.

CHAIRMAN BORER: Right.

DR. THROCKMORTON: They are in the FDA, Dr. Targum's review, Targum's and Friedlin's review on page 30.

CHAIRMAN BORER: Yes, that's --

DR. THROCKMORTON: Oh, I'm sorry, 31 of the review and 32.

CHAIRMAN BORER: That's why I was asking for them to be put up, so we could discuss them.

DR. THROCKMORTON: Right. Those numbers are there.

CHAIRMAN BORER: Do you have a plot of those data? If not, we can go to page 35, the Committee can.

DR. THROCKMORTON: Page 31 and 32 of Dr. Friedlin's and Targum's review, Table 11. It's in the FDA review. It's in the green book.

MEMBER HIRSCH: Since we have spent time looking at subgroups, I think just to put for the record, the numbers are so small that it really is challenging to find a signal in subgroups, isn't it?

DR. THROCKMORTON: But it might be worthwhile looking at the female demographic numbers precisely though. The effect in the women did seem strikingly smaller, again, whether or not other reasons.

CHAIRMAN BORER: Okay. Now --

DR. TEMPLE: It's actually at both doses in that study, too, on page 31.

CHAIRMAN BORER: Right. I don't see any data here and didn't see any data based on racial differences. Do we have any information at all?

DR. WOLFF: We do from the population analysis in which race was not a significant covariate, and so the slope in non-Caucasians was the same as in Caucasians.

CHAIRMAN BORER: How many non-Caucasians were involved in the pivotal trials?

DR. WOLFF: There were fewer than 5 percent.

CHAIRMAN BORER: Okay. Okay. Are there any other issues about efficacy? Bob?

DR. TEMPLE: No. I was just going to say both doses in that study seemed to work less well in women and there was at least a little trend to work better in younger people. Whether one should make anything of that is not clear. The heart failure stuff is interesting, too. Maybe for the future.

CHAIRMAN BORER: Paul?

MEMBER ARMSTRONG: Just one. In some of the early data, you had tracked sinal ischemia with Holter monitoring over time as another robust way of looking at the effects on ischemia. Do you have any information in relationship to the more recent data?

DR. WOLFF: No. We have no Holter data for MARISA and CARISA.

MEMBER ARMSTRONG: Thank you.

CHAIRMAN BORER: Okay. If there are no

other issues, questions to raise about efficacy?

MEMBER NISSEN: I just had one.

CHAIRMAN BORER: Yes.

MEMBER NISSEN: I'm sorry to be persistent, but one more question and that is any studies using anything other than simple exercising testing, such as a nuclear scintigraphy, you know, thallium or Sestamibi scans, exercise echo? If there is any data, now would be a good time to see it, because I think it would help us to understand efficacy.

DR. WOLFF: No, there aren't. Other than the angina frequency and nitroglycerin consumption, which were the other non-exercise endpoints which were assessed and which were significantly reduced in CARISA, we don't really have anything.

MEMBER NISSEN: Okay.

CHAIRMAN BORER: Steve, why would you have wanted to see those kinds of data? I mean, we have seen ST-segment depression data, unless we think they are invalid somehow, because the mechanism by which this drug may act? What difference would it make if

we had --

MEMBER NISSEN: Well, it wouldn't be an approvability issue, but, I mean, the more information there is that amplify upon the robustness, the mechanism. I mean, the fact is is that, you know, many patients today who are being evaluated for ischemia are being evaluated with imaging stress tests and so, you know, while it's not necessarily the standard that the Agency has set for approval, it certainly is meaningful to clinicians to see, for example, a change in a profusion abnormality would be very compelling from my perspective to suggest that there really is something going on there in the myocardium.

CHAIRMAN BORER: Okay. Well, let's go on to the presentation of the safety data.

DR. WOLFF: Okay. So in overview, the integrated summary of safety, which we submitted to support the ranolazine NDA contained data from over 2,700 patients and subjects who were exposed to various formulations of ranolazine for a total of over 1,700 patient-years of exposure. You will see as we

go forward that adverse events on ranolazine are generally dose-dependent and, therefore, manageable by proper dose initiation and titration. And furthermore, we have no evidence for an adverse effect on survival.

Ranolazine has been administered to over 2,700 patients and subjects, over 1,400 of whom received the sustained-release formulation. Of particular note also are the more than 500 patients who were treated with the immediate-release dose of 400 milligrams three times a day. This dose is relevant to the consideration of the safety of ranolazine, because it results in maximum plasma concentrations equivalent to those produced by 750 twice a day and an overall exposure equivalent to that produced by 500 milligrams twice a day.

So if you look at the 1,460 that were treated with sustained-release and the 518 treated, I'm trying to get the slide to advance, there we go, there is almost 2,000 patients that are treated with a dose of ranolazine that is relevant to the analysis of safety and tolerability, which is well in excess of

the 1500 recommended by ICH guidelines. And then, of course, there are other additional exposures with IV and immediate-release, as well.

The duration of exposure is shown here. As I have mentioned, we have had over 1,700 total subject patient-years of exposure to the drug most of which, nearly 1,300 patient-years, was in angina patients on ranolazine SR. The mean duration of exposure of these angina patients to the sustained-release formulation was well over a year at 495 days. 850 have been treated for more than a month, 500 or more for over a year and over 250 for more than two years.

This slide shows the adverse events for MARISA and CARISA, which occurred in at least 2 percent of patients on a given treatment and they were more frequent on at least one dose level of ranolazine than on placebo. Most of these adverse events were reported as mild or moderate in severity and didn't result in discontinuation of treatment. Dizziness, nausea, asthenia and constipation were the most clearly dose related adverse events. Of note is the

500 milligram dose, which you will recall was effective throughout the dosing interval in MARISA. It was very well-tolerated with an adverse event profile quite similar to that of placebo.

Also of note, the increase in adverse events, and particularly the most clearly dose-related adverse events on 1500, was a disproportionate increase going from 1000 to 1500 compared to the generally linear increase in exercise performance. And so, accordingly, we don't recommend the 1500 milligram twice daily dose for clinical use.

This slide gives the rates of sudden death, cardiovascular death and all-cause mortality on ranolazine and placebo from the four month safety update. For each of these three endpoints, the 95 percent confidence intervals around the ranolazine estimates are contained completely within the 95 percent confidence interval around the placebo estimate.

However, there really are relatively few events overall and another confounding factor is that the exposure to ranolazine in this analysis is more

than tenfold that of the exposure to placebo. And so to take a look at these kinds of data in a controlled setting where the duration of exposure to placebo and to ranolazine is more similar, we turn to the controlled studies.

And here we see estimates of mortality on ranolazine versus placebo, in the Phase 2 and 3 IR and SR controlled studies, in the two Phase 3 SR controlled studies and then in CARISA, which was itself the longest double-blind, randomized, placebo-controlled parallel group experience with ranolazine SR in patients with angina. And again, for each of these endpoints, the 95 percent confidence interval lies within or actually exactly overlaps the 95 percent confidence interval for placebo.

In summary then, the efficacy of ranolazine has been demonstrated in five double-blind, randomized, placebo-controlled trials. The drug has been observed to be generally safe and well-tolerated. Those adverse events, which do occur, are generally dose-dependent and, therefore, should be manageable by appropriate dose initiation and titration. And

finally, there is no evidence for any adverse effect of ranolazine on survival. Thank you.

CHAIRMAN BORER: Beverly?

MEMBER LORELL: Even though you are not proposing use of the higher dose, there may be some information useful to the Panel in understanding the dose-dependent increase in the symptom of dizziness. Can you amplify a little bit on what is believed to be the mechanism of that?

DR. WOLFF: Yes, I can, and I will have more data to talk about dizziness and other effects later on in the presentation after Dr. Belardinelli discusses the preclinical electrophysiology, but the dizziness appears to be a central nervous system phenomenon. When you look at the blood pressures of the patients who complain of dizziness, they are actually not lower than the patients who don't complain of it.

And as you will see later when we talk about a controlled overdosing study that we did with IV infusion of ranolazine, the dizziness and nausea are probably kind of the leading edge of a

constellation of symptoms that if you get the plasma concentration higher and higher, begin to include nystagmus and diplopia and even some disturbances of the sensorium and the, you know, complete loss of consciousness, which is reversible completely upon discontinuation and occurs again, I would emphasize, at high plasma concentrations well beyond those necessary for therapy. But the beginnings of that, I believe, is the dizziness that we see at the therapeutic doses.

MEMBER LORELL: I'm sorry. One more quick question while we're on this topic. Was that symptom more or less common or no different in either women versus men or diabetics versus non-diabetics? I know we're slicing and dicing.

DR. WOLFF: No, it's fair to ask. There weren't any generally appreciable differences in the adverse event rates between men and women or diabetics and non-diabetics and, in fact, if we have the adverse events in diabetics, they actually look a little bit better than in the patients without diabetes.

The only place where we saw a difference

in adverse events in the different subgroup where we looked, I think, was relatively predictable. Elderly patients did have more adverse events than younger patients, although the types of adverse events, dizziness, nausea, asthenia, constipation were very much the same, but they happened more frequently in them.

MEMBER LORELL: Thank you.

MEMBER CARABELLO: Do you have any data in heart failure patients with long-term exposure to the drug?

DR. WOLFF: The best data that I could give you would be the data from the safety database in patients with heart failure and those without. We have a look at their adverse events. Here are the data from the Phase 2, 3 controlled SR studies. This is basically MARISA and CARISA and you can see that the adverse events in heart failure are not more common than in the patients without heart failure.

MEMBER CARABELLO: But in those trials, the exposure was relatively short-term?

DR. WOLFF: That's right. And I don't

have them broken out by subgroups for the long-term going forward, but I can tell you when you look at the long-term safety data, we don't see any difference in the pattern of occurrence of adverse events. Dizziness, nausea, asthenia and constipation are the clearly dose-related ones and they tend to occur early if they are going to occur.

MEMBER CARABELLO: My specific concern would be of worsening heart failure. No data to suggest that?

DR. WOLFF: None.

CHAIRMAN BORER: Bob?

DR. TEMPLE: One of the things we said in our letter was that we thought your total safety database for people at relevant doses and reasonable duration was on the low side. Just let me make it clear. We think the number of people exposed for six months and a year is within line of standards and is not a problem. But if you discount people who got single doses, very low doses of the immediate-release, and then the total number of exposures is pretty low.

The ICH suggestion is about 1500. It's

not precise on whether you should include people who got a single dose, but clearly that was not what they had in mind. So this remains on the light side. I think we thought there were about 800 people exposed to relevant doses for at least a month. I just wondered if you want to comment on that. That's about half of what we would usually expect, and I guess I should emphasize if the drug did something really important, you shade that. If it's another of a sort of thing that you already have, you're more interested in a reasonable sized safety database.

DR. WOLFF: Well, the overall database in the ISS, the four month safety update, was 2,783 exposures. So those are the low doses, the single doses, so forth and so on.

DR. TEMPLE: Right.

DR. WOLFF: The sustained-release formulation is the one that we intend to market. There were 1,400 exposures there. It says any exposure and then as you go up to greater than a month, you do lose a lot of them, but that's because you lose all the MARISA patients who got three weeks

of exposure, not a month of exposure.

DR. TEMPLE: Right. No, I know why. I just want to know what you want us to believe about it.

DR. WOLFF: So that's there. And then I do think it's quite relevant to consider the dose for 400 milligrams three times a day, because the plasma concentrations and the exposure are well within the range of what is produced by the sustained-release. And so then --

DR. TEMPLE: Right, but none of those were over 30 days either. Is that right?

DR. WOLFF: That's not entirely true, but it would be difficult for us to know how many were.

DR. TEMPLE: Okay.

DR. WOLFF: Because 400 milligrams three times daily is a dose that was allowed during the Open-Label Follow-On Studies from the immediate-release trials. And we do have patients that went on and were on 400 milligrams three times a day for sometime, but it would be difficult because of the allowance of upward and downward titration. We

weren't able to say exactly how many for more than 30, more than 90 and more than 365, although, they did take that dose in open-label treatment.

CHAIRMAN BORER: Tom?

MEMBER PICKERING: Could you review the data on sudden death? My impression was that about 50 percent of the patients on ranolazine died a sudden death, and that seems to me a rather high proportion, but I don't know what you would expect in this population.

DR. WOLFF: There were 23 sudden deaths out of 56 overall deaths. I think there were 21 of them on ranolazine out of 42 cardiovascular deaths. And I think I would ask Dr. Braunwald to comment on the incidences of sudden death in patients with severe coronary artery disease, but we had half of our cardiovascular deaths that were sudden, and I believe the literature quotes often two thirds of these deaths would be expected to be sudden. Dr. Braunwald?

CHAIRMAN BORER: Alan?

MEMBER HIRSCH: I want to come back to Dr. Lorell's question about the dizziness signal. Even

though you're not looking for an indication at 1500 milligrams twice daily, this is a medication that will be intended to help patients feel better and really what patients are looking for is a subjective sense of well-being. I'm going to ignore all the exercise tolerance, time to ST depression and mechanistic data that demonstrates a real central cardiac effect.

So I want to ask what is the meaning of the dizziness in the absence of any clear blood pressure change or rhythm disturbance, and I think you have implied that this is interpreted to be a CNS effect?

DR. WOLFF: Correct, yes.

MEMBER HIRSCH: So my question is if we know that there is a potential signal somewhere between maybe 1000 and 1500 milligrams in the CNS, is there any other information on other more robust measures of how this medication might affect cognitive function? In other words, really, is there any effect in the sensorium on cognitive function marketed to a large group of Americans sort of like the statin motif? There may be questions about beyond the

classic AE description of what it does to cortical function.

DR. WOLFF: Well, I can't really speak with clinical data to cognitive function, because that was never formally assessed. What I can do is amplify on my prior response about how this appears to be part of a constellation of symptoms. And you can see here that average ranolazine concentration in patients that are having some of these adverse symptoms that we believe are part of the CNS constellation.

Now, to put this into perspective, recall, and I don't know if you can recall, I'm not sure I have told you, but the average plasma concentration on the top dose that we recommend of 1000 milligrams twice a day is 2,500. And so 3,200 is already over the mean concentration. The 95 percent upper limit for patients treated with 1000 bid is on the order of around 5,000. So you're at the high end here anyway.

And so this is the average concentration in patients who complained of nausea and vomiting. Here, dizziness and vertigo. Here are the patients with syncope. Here are the patients with abnormal

vision and diplopia. And by the time you get to the clearly CNS-related effect of paresthesias and confusion, the plasma concentration is more than twice as high on average.

So as I say, I think there is some degree of nausea. Well, we clearly see dose related nausea and dizziness at the higher end of the recommended dose range in some few patients, but I don't think that you get clearly into the CNS until you get to higher concentrations.

CHAIRMAN BORER: Tom?

MEMBER PICKERING: On the same lines, do you have any information about depression, which is obviously a problem in this group, but is something the patient might not volunteer unless asked?

DR. WOLFF: We don't have anything perspective that way.

CHAIRMAN BORER: Doug?

DR. THROCKMORTON: Yes, just a small point on the syncope and the dizziness. I guess Andy will be talking about that a bit more, but the package that you received this morning included an analysis from

the FDA on the relationship between serum concentration and the reported incidence of dizziness and syncope and that's on pages 35 and 36 of that document if you're interested. There appears to be a curvolinear relationship at least in some circumstances.

The other thing, Dr. Wolff I guess will be getting back to this, the attribution of the source of this syncope and the dizziness and things like that. You're attributing it to a central effect. You know, that will be interesting. There are, of course, reported effects of ranolazine on the alpha adrenergic receptors and things like that that at least raise the possibility of other mechanisms, as well.

DR. WOLFF: Yes, and we will address that later.

CHAIRMAN BORER: Okay. Steve is our Committee reviewer, but before he gets started on his inventory, I want to make one point and obviously, Bob and Doug can comment on or modify this if you like. We're being asked to consider a drug for the prevention of angina, not to prolong life, not to

prevent myocardial infarction, not to do anything else, but to prevent angina. If there are symptoms that are caused by the drug that aren't importantly dangerous, that don't constitute serious adverse events, totally different issue, and I think Steve will get into that and we all will as we go into the QT issues.

If there are other adverse events that are not serious, not imminently life threatening, the presumption is that a patient can determine whether the reduction in angina, if it occurs, is more important to him or her than the adverse event. So while I think we have to know about these quality of life issues, I think we have to consider this application in that context. I mean, this is a drug for the prevention of a symptom, not for anything else.

Now, if it's doing harm, that's a different issue and serious harm and, of course, we have to understand the extent to which it is or it isn't or might. With that having been said, Steve, why don't you go ahead?

MEMBER NISSEN: Okay. Yes. I'm going to hold a lot of safety questions until we get to the later portions, but I had a few of them. Let me test a hypothesis on you just for a second. Would you agree with me that we have a drug here that has a fairly narrow therapeutic index? That is at doses that are 1.5 or certainly two times the recommended dose, patients tend to get into a lot of side effect problems. Would that be a fair statement?

DR. WOLFF: I don't know that I would agree that there are a lot of side effect problems. I think that you can see a dose relationship and we do agree that 1500 is a dose higher than we would recommend use.

MEMBER NISSEN: Yes. I know you must agree, because you are obviously not asking us for approval for a 1500 milligram dose.

DR. WOLFF: Right, right.

MEMBER NISSEN: So, you know, 1000 is the efficacious dose. 1500 was not acceptable, and so we are talking -- I mean, some drugs that we administer to patients have, you know, fairly wide therapeutic

index. Some of them have a fairly narrow one. That's not necessarily a huge approvability issue, but it is a characterization that I think would be correct. Would you agree?

DR. WOLFF: We would agree that the appropriate dose range for most patients is 500, 750, 1000 milligrams twice a day.

MEMBER NISSEN: So what I want to understand and explore is a concern for me that I need reassurance about, is that I have a sense for who I think is likely in this country to get the drug, and let me see if I can describe it. You know, first of all, younger patients, patients who are, you know, in the, you know, middle ages and maybe even the young-old tend to get treated very aggressively with revascularization and other strategies. Older, frailer, sicker patients, maybe those that are beyond revascularization are the ones most likely to get the drug at least initially, and I have a bunch of them in my patient population. They tend to be diabetes. They have had a couple of bypasses. They still have angina. They are not doing well.

They also are, however, patients that tend to be much frailer, somewhat older, have more concomitant diseases, such as hepatic or kidney disease, etcetera. And so one of the things that we need to understand, I think I want to make sure the Committee understands, because I read this massive amount of documents that we got from the FDA, in fact, I am going to be filing a Workmen's Compensation claim for carrying all this stuff around for a few weeks, is that there is some evidence here that patients with liver disease and kidney disease, for example, have elevated serum concentrations.

And I would like you to share with the Committee the relationship between these concomitant conditions and the elevations of serum levels, because if levels are going to be one and a half or two times higher in patients with concomitant, other organ system disease, we need to know about that as we consider the safety profile.

DR. WOLFF: Yes, we will address that specifically this afternoon.

MEMBER NISSEN: Okay. All right. Fine,

then I will hold on that. But I just want to make sure we get to review the relationship between serum concentrations and concomitant diseases. And that also includes concomitant drugs?

DR. WOLFF: Yes, it does.

MEMBER NISSEN: Okay.

DR. WOLFF: I will treat them both this afternoon or later on today.

MEMBER NISSEN: Okay. Then that helps a little bit, because I think we can move along toward our break.

The syncope issue. There were a couple of dozen patients or so that had syncope. And what do you know, what do we know about the patients that had syncope? Would any of them have syncope during electrocardiographic monitoring?

DR. WOLFF: Yes, some of them did, in fact, some of the subjects. This all actually comes up later.

MEMBER NISSEN: Okay.

DR. WOLFF: But I would be happy to answer that now.

MEMBER NISSEN: Yes.

DR. WOLFF: I mean, because it's a simple answer, yes.

MEMBER NISSEN: Yes.

DR. WOLFF: Several of the subjects in the Controlled Overdose Study that I will present later on where we infused the drug to the highest concentrations literally that patients could tolerate, did have events that coded to the term syncope while they were being electrocardiographically monitored continuously and they were just in sinus rhythm, which is more the reason why we believe this is a CNS effect at these very high concentrations.

MEMBER NISSEN: Did their blood pressures fall?

DR. WOLFF: No.

MEMBER NISSEN: Did anybody have syncope?

DR. WOLFF: Some component of an alpha-1 adrenergic effect and postural hypotension though can also be a component of syncope, and if we get more into syncope, I think it might be useful to wait until --

MEMBER NISSEN: Okay. We will wait. But I do want to see also about whether there was any interaction with sublingual nitroglycerin. In other words, if you have angina on ranolazine and you take a sublingual nitro, are you more likely to go to ground than somebody who is on placebo? I mean, that's a question that would obviously come up for clinicians to know about, is whether that would occur.

DR. WOLFF: What's true is that among the 38 patients who had syncope, their use of vasoactive medications in general, ACE inhibitors, long-acting nitrates, calcium channel blockers and alpha-1 blockers was about twice that in the overall patient population. So a third of the patients that had syncope roughly were on two other vasoactive medications known to be associated with syncope and another third were on three or more.

MEMBER NISSEN: So there is some issue of potentiation of the effects of those agents by ranolazine?

DR. WOLFF: Well, there was more use of vasoactive medications in the patients who had

syncope.

MEMBER NISSEN: All right. With that in mind, I think, you know, since we are going to hear much more about the pharmacokinetic and other interactions, maybe we ought to just table this and kind of move along.

CHAIRMAN BORER: Okay. Beverly?

MEMBER LORELL: A quick clarification. In that interesting and helpful slide you showed us of the spectrum of CNS side effects, was that drawn from the deliberate excess dosing study that you're going to talk about this afternoon or was that from the two pivotal trial experience that we're discussing this morning?

DR. WOLFF: I believe that was from a population that included the overdose study, as well as the pivotal trials. It was from ISS. It was from the -- so is this from the four month safety update then or is it from the original NDA ISS?

UNIDENTIFIED SPEAKER: NDA.

DR. WOLFF: Okay. So this is from the ISS safety database then, that slide. So that has got

angina. It has the Phase 2, 3 studies. It has got the immediate-release studies. It has the Controlled Overdose Study, as well.

CHAIRMAN BORER: Okay. We'll stop here and take a break until 10:30 and then we'll resume.

(Whereupon, at 10:17 a.m. a recess until 10:33 a.m.)

CHAIRMAN BORER: Okay. It's 10:34. You have gotten four extra minutes, so we're going to begin. Dr. Wolff?

DR. WOLFF: Yes?

CHAIRMAN BORER: Andy, do you want to have Peter Kowey begin? Is that the next presentation?

DR. KOWEY: All set, Jeff? Dr. Borer, members of the Advisory Committee, Ladies and Gentlemen, my name is Peter Kowey. I am from Mainline Heart Health Center in Philadelphia. The sponsors presented efficacy and safety data this morning from a number of well done clinical trials for a drug that has a novel pharmacodynamic effect.

Clearly, the drug has the potential to fill the unmet medical need described by Dr.

Braunwald. The major impediment to its approval and acceptance is its QT interval effect and its putative risk of causing torsade de Pointes. FDA and the sponsor felt that this issue needed to be addressed comprehensively. That has been accomplished. My job is to preview that information and to put it into some kind of context for the Committee.

In fact, three parallel approaches were taken and will be presented by subsequent speakers. The first was a comprehensive preclinical assessment. We realize that preclinical data of this nature is not a common presentation to an Advisory Committee of this kind. However, we think that it's critically important in understanding the torsade potential for this particular drug.

Dr. Belardinelli, who will come to the podium after me, will share some of his vast experience and that of several internationally renowned scientists. Included will be work with the model that has been employed in our basic electrophysiology laboratory that makes use of the myocardial wedge preparation. Our experience has been

that use of the myocardial wedge in a female rabbit provides an exquisitely sensitive assessment of the risk of torsade.

Dr. Belardinelli will further orient you to this model. In essence, this model allows us to measure three very important electrophysiological parameters. In addition to QT interval measurement, the model also allows us to measure a parameter called transmural dispersion of repolarization, which we will be referring to as TDR. This means that there is a difference or a potential difference in repolarization across the thickness of the myocardial wall. You may regard that as a substrate for the development of torsade.

The model also allows us to assess the possibility of there occurring early afterdepolarizations, so it's for potentials which occur during Phase 2 of the action potential. These potentials can be thought of as the triggers for torsade de Pointes. In many cases, you can think of this as the precursors of torsade.

On this slide we examine the effect of

several agents known to prolong the QT interval on these three parameters that I just described. In general, drugs that prolong the QT interval and prolong transmural dispersion of refractoriness also cause early afterdepolarizations.

There are two exceptions. One is a drug with which I'm sure most of the people on the Panel are very familiar, amiodarone, which does not cause early afterdepolarizations and for which torsade de Pointes is considered a decidedly rare event. The other exception to the rule is ranolazine, which causes neither transmural dispersion of repolarizations or early afterdepolarizations in this very sensitive model that I have described.

Preclinical data, no matter how comprehensive and compelling, can never be relied upon to tell the entire story with regard to the risk of lethal arrhythmias. In lieu of an impossibly large clinical trial to count actual torsade events, we need a surrogate. The FDA has chosen the QT interval to be that surrogate. I have been heard to say not only in other venues, but while sitting at a table just like

that, that the QT interval is a poor surrogate for what we really want to know.

There are many reasons why we believe the QT interval was not a great surrogate. One has to do with the variability of the measurement itself. Another has to do with changes in QT interval under diverse physiologic conditions, and there are very mundane issues with the QT interval, including how to correct for changes in heart rate.

Nevertheless, it is the best we have and the truth is that the magnitude of QT prolongation does appear to correlate with the risk of developing torsade. Dr. Wolff following Dr. Belardinelli will return to the podium after the preclinical talk to show you the QT data on ranolazine. I believe that you will agree after you see that information that the magnitude of the central tendency change with ranolazine is akin to what has been seen with other drugs that are regarded to have a low or a very low risk of causing torsade, and I believe that the outlier analysis that you will see will convince you of the same thing.

The third element of QT risk assessment is the counting of clinical events. As I said, there have been no cases of torsade described and there have been no clinical events that could be interpreted as a complication of QT interval prolongation. Once again, Dr. Wolff will present information with regard to pertinent clinical events in his presentation that will follow Dr. Belardinelli.

Therefore, the assessment of the risk of torsade should be appreciated as a multifaceted and highly complex undertaking. We would love to be able to show you an adequately sized clinical trial in which episodes of torsade could be counted in patients who receive drug versus a positive comparative or a placebo. But the truth of the matter is that the number of patients that would need to be included in such an analysis is prohibitive.

We agree that the QT interval is an adequate surrogate, but we also believe that a very large and robust preclinical package supplements the information regarding the QT interval and provides independent information regarding this putative risk.

I believe that the data set that you are about to see represents by far the most sophisticated data set with regard to the question of QT interval prolongation and risk assessment and should represent, in truth, a paradigm shift with the way we consider the risk of drugs that prolong the QT interval and their potential for causing malignant ventricular arrhythmias.

Jeff, unless there are some questions, I would very much like to bring Dr. Belardinelli to the podium to follow this.

CHAIRMAN BORER: Yes. I think we'll run through the entire presentation on QT and arrhythmias and then perhaps we can ask whatever questions we have. And, Peter and Andy, I would urge you since I'm looking out in the audience and I see John Camm and Jeremy Ruskin and Dan Roden and Craig Pratt, and there may be others I don't see who are, in addition to yourself, highly respected experts in this area who we all know, I would suggest, if you want, make liberal use of them in answering any of the questions that we may have.

DR. KOWEY: You betcha.

DR. BELARDINELLI: Mr. Chairman, Committee members, Ladies and Gentlemen, today I will describe some of the effects of ranolazine on ventricular repolarization. But before I do that, I would like to start by showing some animal data that demonstrates that the QT interval prolongation is not the sole determinant of the potential of a drug to cause torsade.

In this slide on horizontal axis is the magnitude of the increases in QT interval by various drugs, and on the vertical axis is the respective incidence of torsade de Pointes in a canine model that is highly susceptible to the induction of this arrythmia. Note that equal prolongations of the QT interval by d-sotalol and dofetilide, that is 55 milliseconds, resulted in markedly different incidence of torsade, a 5 percent for d-sotalol and 67 percent for dofetilide.

On the far right we have amiodarone and almokalant. Both prolong QT interval by about 70 to 75 milliseconds. Whereas, amiodarone in this model did not cause torsade, almokalant did in,

approximately, 64 percent. Based on this animal data and other data, prolongation of QT interval is not the sole determinant of the potential of a drug to cause torsade.

Therefore, in addition to QT interval, other markers of pro-arrhythmia are needed. Depicted on this slide are the major electrophysiological events known to play a role in the genesis of torsade de Pointes, from herein simply torsade.

Drugs that reduce the repolarizing potassium current, IKr, cause prolongation of ventricular action potential and, consequently, of the QT interval. This increase in action potential duration may lead, but not always, to two arrhythmogenic events. They are the induction of early afterdepolarizations, EADs, and to increases in the dispersion of ventricular repolarization from, herein referred simply as, dispersion.

Therefore, EADs as the trigger and increasing dispersion as the substrate are key events in the initiation and perpetuation of torsade de Pointes. Before I describe the effects of ranolazine,

I will tell you a little more about the roles of EADs and increased dispersion of ventricular repolarization on the genesis of torsade.

EADs give the rise to ectopic beats that is extrasystoles. The prolongation of the action potential duration facilitates the induction of EADs, which give rise to ectopic beats that in turn initiate torsade. Shown on the right is a prolonged action potential with two EADs that give rise to two ectopic beats on the surface electrocardiogram. When inward depolarizing currents, such as sodium and calcium, are increased they generate the upstroke of EADs. Hence, inhibition of IKr prolongs the action potential. Whereas, the reactivation of the inward currents would elicit EADs.

Therefore, drugs that prolong the action potential duration while EADs are in use may generate ectopic beats and thus, have the potential to cause torsade. Shown in this slide are the differences in action potential duration across the left ventricular wall. Depicted is a transmural wedge of the left ventricle and representative action potentials from

the epicardium, mid-myocardium and endocardium.

The numbers on the right are the action potentials in milliseconds and not shown, the QT interval is the composite of these action potential durations from all ventricular cells. But importantly, note that the action potential duration of the mid-myocardial cells is longer than that of the endocardial and epicardial cells. In this example, this maximal difference is 59 milliseconds. Thus, the dispersion is 59 milliseconds.

The normal differences in action potential duration that you see here when increased, for instance by drugs, create a substrate for arrhythmias. An example is shown next. Drugs that inhibit IKr, such as sotalol, cause greater prolongations of the action potentials of the mid-myocardium than either the epicardium or the endocardium. Consequently, the dispersion is increased to 98 milliseconds. Therefore, drugs that accentuate the normal dispersion of ventricular repolarization create a substrate for arrhythmias and not surprisingly had been found to be pro-arrhythmic.

The strategy used to assess the potential pro-arrhythmia risk of ranolazine was based on the electrophysiological events associated with drug induced torsade. Hence, we determined the effects of ranolazine on ion currents, on the ventricular action potential in QT intervals, induction of EADs and fourth, the dispersion of ventricular repolarization.

Experiments were carried out in preparations at such doses listed here on the left. Very importantly, they were carried out under conditions known to increase the risk for torsade, such as bradycardia, hypokalemia, pharmacological of ion channel mutations in diseases. First, I will describe the effects of ranolazine on ion currents. I will only report to you on the two most sensitive currents to ranolazine, the outer current, IKr, and the inward current, late INa.

Inhibition of IKr leads to the lengthening of the action potential and hence, prolongs the QT interval. Ranolazine inhibits this current with a potency of 12 micromolar. On the other hand, inhibition of late INa leads to a shortening of the

action potential and, consequently, shortens the QT interval. Ranolazine inhibits late INa with a potency as low as 5 micromolar.

The inhibition of late INa is expected, therefore, to counterbalance the arrhythmogenic effects of the inhibition of IKr, such as induction of early afterdepolarizations. Ranolazine, you already heard, prolongs the action potential and QT interval, but in contrast, through IKr blockers, this effect is not heart rate-dependent.

Drugs that inhibit IKr often cause greater prolongation of the action potential in QT interval at slow heart rates than a fast heart rate. This is relevant, because you know that bradycardia is a major factor for drug induced torsade. Shown in Panel A is the relationship between pacing rate and the prolongation of the monophasic action potential.

The IKr blocker E-4031 caused a 40 millisecond prolongation of the action potential when the rate was fast, that is 150 beats per minute, but caused a much greater effect, almost double, when the rate was slow, 60 beats per minute. In contrast, 5

micromolar ranolazine caused the same prolongation of the action potential whether the pacing rate was fast or slow. The slope of this relationship for ranolazine was near zero, that is was rate independent, whereas the slope for E-4031 was much steeper.

Shown now in Panel B is a bar graph of these slopes, of the relationship between QT interval and heart rate in humans before and after administration of E-4031, dofetilide and ranolazine. Similar to the results in isolated hearts, the slope of this relationship, i.e., between QT and heart rate for ranolazine was near zero. Whereas, the slope for E-4031 and dofetilide were much steeper. Therefore, during bradycardia the prolongation of QT interval by ranolazine would not be exaggerated.

Using seven different types of cardiac preparations and the numerous conditions that I listed earlier for you, known to increase the risk of torsade, EADs did not occur in the presence of ranolazine. On the contrary, as summarized here, ranolazine reverses the action potential duration

prolongation and suppresses EADs and ventricular tachycardia caused by one, IKr blockers, such as sotalol and E-4031, two, the IKs blocker, chromanol, and three, the late sodium current enhancer, the anemone toxin, ATX-II, all known to mimic the ion channel dysfunctions associated with long QT syndromes. Therefore, ranolazine does not induce EADs, ectopic beats or torsade. It suppresses the arrhythmogenic activity caused by other QT prolonging drugs.

Next, I will show an example with sotalol followed by an example with E-4031. Shown in green is a controlled action potential recorded from a Purkinje fiber and now in blue is an action potential with a large EAD recorded after the application of d-sotalol. Still in the presence of this sotalol, 5 micromolar of ranolazine suppressed the EAD and shortened the action potential. 10 micromolar ranolazine caused an additional shortening of the action potential. This effect that I am showing here to you of ranolazine was also observed in cardiomyocytes and in whole hearts when EADs were induced by quinidine, the anemone toxin

by E-4031 and other drugs.

Next, I will show you an example with E-4031 in a female rabbit heart. The rabbit, in particular, the female rabbit heart is exquisitely sensitive to the arrhythmogenic effects of QT prolonging drugs. Shown in Panel A here are monophasic action potentials recorded during controlled conditions. As mentioned earlier, bradycardia in long pauses are risk factors for torsade. In this experiment, the heart was paced at a constant rate of 60 beats per minute except when a three-second pause was introduced to sensitize the preparation to the arrhythmogenic effects of QT prolonging drugs.

As you can see, under controlled conditions following the pause, no arrhythmic activity was noted. In Panel B, ranolazine at a concentration that is sixfold higher than the upper limit of its therapeutic range. As expected, it prolonged the action potential, but importantly, following the pause, neither EADs nor any other arrhythmic activity was observed.

In Panel C in the presence of E-4031 following the pause, EADs in short runs of ventricular tachycardia were observed. Now, in Panel D, 5 micromolar ranolazine still in the presence of E-4031 abolished the arrhythmic activity caused by E-4031. Therefore, ranolazine does not induce EADs, does not induce ectopic beats or initiate ventricular tachycardia, whereas, E-4031 does. On the contrary, as shown here in Panel D, ranolazine suppresses the arrhythmogenic activity caused by E-4031.

Ranolazine, unlike drugs that cause torsade, does not increase dispersion. Specifically, it does not increase transmural dispersion of repolarization, TDR. As can be seen in contrast, d-sotalol and the toxin ATX-II caused large increases in dispersion, 83 and 123 milliseconds respectively, both known to cause torsade.

To further evaluate the effect of ranolazine on dispersion, experiments were carried out during hypokalemia, a condition well-known to be a risk factor for torsade. The results are now summarized. Similar to the results at normal kalemia,

during hypokalemia, that is 3 millimolar, and as low as 2 minimolar extracellular potassium, ranolazine at a concentration ranging from 1 to 100 micromolar caused no significant changes in TDR.

But very importantly, irrespective of the extracellular potassium concentration be it for 3 or 2, in the presence of ranolazine transmural dispersion remained below 40 milliseconds, that is within the normal range, and there were no EADs nor arrhythmias. EADs and increases in dispersion of ventricular repolarization predict the occurrence of torsade in humans. Listed in the table are drugs known to inhibit IKr, prolong the action potential in QT interval. Pentobarbital and ranolazine are two drugs that have not been reported to cause torsade in humans.

On the other hand, quinidine, d-sotalol, terfenadine, erythromycin and cisapride have all been reported to cause torsade in humans, and found to be capable of inducing EADs and increasing transmural dispersion of repolarization. Thus, ranolazine does not induce EADs nor increase transmural dispersion in

a preparation that other drugs known to cause torsade do induce EADs and do increase transmural dispersion of repolarization.

In summary, drugs that cause torsade de Pointes do so by inducing EADs in accentuating the dispersion of repolarization present in the normal heart. Ranolazine prolongs the action potential duration in QT interval, but it does not induce EADs nor does it increase dispersion. On the contrary, ranolazine suppresses the arrhythmic activity effect of a number of QT prolonging drugs. Therefore, ranolazine would not be expected to cause torsade de Pointes.

CHAIRMAN BORER: Okay. Thank you very much. Are you going to present anymore formal?

DR. WOLFF: Thank you, Dr. Borer. Well, now, having examined the basic electrophysiological properties of ranolazine, let us now then turn to our clinical characterization of the effect of ranolazine on ventricular repolarization.

As you will see, the effect of ranolazine on the QTc interval has been very well-characterized

throughout and even beyond its therapeutic range, including plasma concentrations up to 10,000 nanograms per mL and exceeding tolerability. Throughout this entire range, the relationship between the ranolazine plasma concentration and the change in the QTc remains linear at about 2.4 milliseconds per 1000 nanograms per mL.

Thus, over the recommended dose range of 500 to 1000 milligrams twice daily, the average increase of QTc on ranolazine is 2 to 5 milliseconds and it remains less than 20 milliseconds or about equal to it on average during maximal inhibition of the major elimination pathway of ranolazine, cytochrome P450 3A4, by ketoconazole. And as Dr. Belardinelli has just demonstrated, the cellular electrophysiology underlying the QTc prolonging effect of ranolazine is fundamentally different from that of drugs, which prolong the QT and which are known to cause torsade.

Our database contains over 25,000 QT measurements from nearly 2,400 subjects and patients treated with ranolazine for a total of 1,700

subject/patient-years. Again, over 250 patients have been followed for over two years with serial electrocardiograms. All the electrocardiograms obtained in CVT-sponsored studies have been read under the direction of Dr. Bernard Chaitman at the single core laboratory in St. Louis University. I will also present the results of the population QTc analysis that included nearly 16,000 pairs of QTc measurements and simultaneous steady-state ranolazine plasma concentrations.

This slide summarizes the study designed for CVT 3111 in which we evaluated the effects of ranolazine on the QTc interval during intravenous infusion of the drug to the limits of tolerability. In effect, this was a controlled overdosing situation. A total of 16 women or, I'm sorry, 16 men and 15 women were enrolled into a study, which was planned to achieve target ranolazine plasma concentrations of 4000 nanograms per mL, 10,000 nanograms per mL and 15,000 nanograms per mL. For perspective, 4000 nanograms per mL then is at the upper end of the distribution of concentrations achieved with our

highest proposed dose of 1000 milligrams twice daily.

10,000 nanograms per mL is a concentration higher than was observed in any of the chronic angina patients receiving 1000 milligrams twice a day in MARISA or CARISA and 15,000 milligrams was chosen as the target plasma concentration, which we had, at that time, never achieved in any subject or patients.

All subjects and patients or all subjects under a single-blind infusion for 24 hours and then there was a double-blind infusion where most of the subjects got ranolazine and some got placebo. As you can see, vital signs, samples for measurement of ranolazine plasma levels and electrocardiograms were obtained very frequently both during single-blind placebo infusion, as well as during double-blind treatment.

Of note, only seven patients received the infusion targeting the 15,000 nanograms per mL dose. The trial was discontinued after the treatment of those seven subjects, because intolerable symptoms developed in each of them and the sponsor and the investigators agreed it would not be ethical to

continue to expose additional subjects to that treatment.

Here are the data from CVT 3111. First, notice that the range of variability in the absence of ranolazine on placebo encompasses the entire range of changes seen during treatment with the drug. We did achieve a broad range of plasma concentrations in the study. Here these lines represent the 50th percentile of concentrations achieved on 1000 milligrams twice a day in MARISA and CARISA. Here at about 5500 is the 95th percentile for that population and here is the highest concentration that was achieved in MARISA and CARISA.

Thus, CVT 3111 studied a range of concentration, which exceeded those likely to occur during treatment of chronic angina patients even at the highest proposed dose of 1000 milligrams twice a day. As I mentioned before, the target plasma concentration of 15,000 nanograms per mL, which would have been out here somewhere, couldn't be achieved in any subject because of dizziness, nausea, postural hypotension, diplopia, somnolence, syncope and

paresthesia.

Of note, the QTc was never observed to increase by more than 60 milliseconds from the baseline in this study. Overall, the relationship between the plasma concentration and the QTc was linear throughout this entire range of concentrations with a slope of 2.29 milliseconds per 1000 nanograms per mL. And I think I better have a little water here.

So our conclusions from CVT 3111, the controlled overdosing experiment, was that the relationship between the plasma ranolazine concentration and the QTc remains linear with a slope of about 2.29 milliseconds per 1000 nanograms per mL over the entire achievable concentration range, and that plasma concentrations approaching 15,000 nanograms per mL are unlikely to be tolerated by angina patients in clinical practice, because that concentration could not be achieved or really even approached in the study.

And finally, syncope was observed at high plasma concentrations in this study during continuous

electrocardiographic monitoring with no evidence of arrhythmia. The findings from CVT 3111 were confirmed and extended in a population analysis that combined nearly 16,000 pairs of QTc measurements and steady-state plasma concentrations from over 1,300 subjects across 15 different studies.

Once again, the slope of this relationship was observed to be linear with a similar value from that obtained in CVT 3111 of 2.4 milliseconds per 1000 nanograms per mL. This slope was not altered by the heart rate, by the patient's sex, by the presence of heart failure, by treatment with diuretics, by the patient's age or by the absence, presence or type of background anti-anginal therapy.

This is a very different phenotype from what is observed on drugs, which prolong the QT interval and are known to cause torsade de Pointes. Several of those other drugs have been reported to cause larger changes in women for a given plasma concentration and in patients with heart failure. The slope of this relationship was found to be somewhat steeper in patients with hepatic impairment.

Outlier values were generally infrequent and sporadic. Consistent with the population analysis, changes from baseline greater than 60 milliseconds were more obviously related to the dose that were absolute values greater than 500 millisecond. It's noteworthy that these outlier value rates reflect a much larger number of ECGs per patient than is often submitted in a safety database with outlier patients having experienced 14 to 15 ECGs per patient on average. It's also noteworthy that the duration of treatment and the number of ECGs per patient obtained on treatment is substantially greater than that for placebo, which comes solely from the controlled experience while these contain measurements from long-term open-label follow-up.

As we characterize the ranolazine plasma concentration as a major determinant of the QTc effect, we have in turn characterized the determinants of the ranolazine plasma concentration. The kinetics of ranolazine are generally unaffected by the patient's sex or age, by the presence or absence of food and by common comorbidities, such as congestive

heart failure and diabetes. Atenolol, amlodipine, digoxin and simvastatin do not affect ranolazine plasma concentration. Because the major elimination pathway is known to be cytochrome P450 3A4 with some contribution from cytochrome P450 2D6, a number of formal drug-drug and drug-disease interaction studies were undertaken, which are summarized on the next slide.

The most extreme condition we found was complete inhibition of the major elimination pathway, cytochrome P450 3A4 with ketoconazole at 200 milligrams twice a day. This resulted in roughly a fourfold increase in plasma concentrations as you can see here, and the increase in QTc was proportional. Accordingly, as the average increase in the QTc on 1000 milligrams of ranolazine twice daily is about 5 milliseconds in the absence of ketoconazole, during this study the average increase in QTc on the combination of ranolazine and ketoconazole was 20 milliseconds.

The recent preliminary concept paper regarding the evaluation of the effects of drugs on

the QTc interval advises particular attention to the adverse events shown on this slide. We have already discussed dizziness as a very clearly dose related phenomenon observed in the Phase 3 studies and, especially, along with other central nervous system symptoms at high concentrations in the Controlled Overdose Study, CVT 3111.

None of these others appear in a dose related pattern, except possible syncope, which occurred in five patients that were randomized to direct treatment with 1000 milligrams twice daily in CARISA and to three patients receiving randomized treatment with 15,000 milligrams twice daily in MARISA.

So let's then consider the issue of syncope in a bit more detail. Syncope on ranolazine appears to be related to postural hypotension at higher doses. The occurrence of postural blood pressure changes in healthy volunteers is a clearly dose related phenomenon, especially when they have been treated with doses as high as 2000 milligrams twice daily during early dose defining clinical

pharmacology studies of the sustained-release formulation.

During those early trials, some of those volunteers were sufficiently orthostatic to be unable to stand up for vital sign measurements at the peak effect of these very supra-therapeutic doses. This orthostatis is consistent with a weak alpha-1 adrenergic receptor antagonism that becomes apparent in nonclinical pharmacology studies at the upper end of the therapeutic concentration range and beyond.

Similarly, as mentioned earlier, syncope was observed in a Controlled Overdosing Study, CVT 3111, in the absence of arrhythmias during continuous electrocardiographic monitoring. The chronic angina patients, as we discussed this earlier actually, who experienced syncope in the Phase 2, 3 controlled trials and their open-label follow-on were more likely to be taking other vasoactive medications that are also known to cause syncope. And I think I said earlier about a third of them were on two such medications and another third of those who experienced syncope were on three or more. And finally, there was

no electrocardiographic evidence for torsade de Pointes in any patient on ranolazine, including the ones with syncope.

Overall, the rate of syncope on ranolazine is about 2 percent per patient-year of treatment, which is similar to that given in the labeling for other alpha-1 adrenergic blockers. The placebo rate appears to be lower. However, once again, the experience on ranolazine is more than tenfold greater than the experience on placebo and, as a consequence, once again the 95 percent confidence interval about the ranolazine estimate fits completely within the 95 percent confidence interval for the placebo estimate.

In summary then, the effect of ranolazine on the QTc interval has been well-characterized throughout and beyond the range of tolerable plasma concentrations remaining linear throughout this range at about 2.4 milliseconds per 1000 nanograms per mL. Even with controlled overdosing in Study CVT 3111, we have been unable to achieve a plasma concentration approaching 15,000 nanograms per mL, which indicates that intolerability will tend to prevent exposures to

plasma concentrations associated with larger QTc increases. And finally, as we heard earlier from Dr. Belardinelli, the cellular electrophysiology underlying this QTc effects is fundamentally different from that of drugs, which prolong the QT and which are known to cause torsade.

Having considered then the efficacy, safety and electrophysiological profile of ranolazine, a rationale for dosing can be constructed. We have shown the ranolazine plasma concentration to increase with dose and in turn, the efficacy to increase linearly from 500 to 1,500 milligrams twice daily in MARISA and with the plasma concentration in a large and robust population analysis. In contrast to the generally dose and concentration dependent increase in efficacy, adverse events increase disproportionately from 1000 milligrams twice a day to 1,500 milligrams twice a day.

Accordingly then for most patients, we propose dosing should begin at 500 milligrams twice a day with upward titration as needed according to the clinical response through 750 milligrams twice a day

to 1000 milligrams. For patients with severe renal disease, hepatic impairment or those taking higher doses of diltiazem or verapamil, a lower dose range of 375 to 750 milligrams is recommended. Thank you.

CHAIRMAN BORER: Dr. Ruskin?

DR. RUSKIN: Dr. Borer, Committee members, ladies and gentlemen, I'm Jeremy Ruskin and I would like to offer some brief concluding comments about the benefit risk assessment of ranolazine. As you've heard, many patients face recurred episodes of angina that limit their physical activity and significantly impair their quality of life. Epidemiologic data suggests that a significant minority of patients with angina are not adequately treated with available therapies and would benefit from additional pharmacological options.

As you've also heard, a year after PCI resurgery for the relief of ischemia, as many as 20 percent of patients still experience angina pectoris despite the fact that as many as 80 percent of them are still taking anti-anginal medications. Familiar to everyone in this audience are the limitations to

uptitration of currently available anti-anginal drugs and these include bradycardia, hypotension, fatigue and/or depression for beta blockers, bradycardia, hypotension and left ventricular dysfunction for calcium channel blockers and headache, hypotension and the need for a drug free interval with nitrates.

Ranolazine has the potential to offer benefit in all of these situations. As you've heard, ranolazine is a novel agent that is pharmacodynamically distinct from other anti-anginal drugs. At standard therapeutic concentrations it is hemodynamically neutral with no significant effect on heart rate, blood pressure or ventricular function. And the drug is safe and effective both alone or in combination with other anti-anginal drugs.

Ranolazine also demonstrates consistent benefit across a broad spectrum of patient cohorts including those with heart failure, diabetes, lung disease, prior myocardial infarction or revascularization, as well as in patients with borderline heart rates or blood pressures, and the drug is effective in these cohorts both alone and in

combination with other anti-anginals.

This slide summarizes for you the mean increases in placebo corrected exercise times observed with ranolazine, as well as with three other anti-anginal drugs. And although this comparison is subject to the limitation of cross study comparisons, it is interesting to note that the effect size observed with ranolazine is quite similar to that observed with atenolol, diltiazem and transdermal nitroglycerin. And this is occurring in the setting of ranolazine being tested in patients with severe angina pectoris and markedly limited exercise tolerance.

With regard to safety, the adverse effects of ranolazine are generally mild to moderate with no serious organ toxicity. Discontinuations are infrequent and when the option arose a large preponderance of patients elected to continue therapy with ranolazine. There are drug-drug interactions, but these are well-characterized and most important for today's discussion, as you've heard, ranolazine does have a concentration dependent effect on the QTc

interval.

These two graphs compare for you the effects on QTc of ranolazine and terfenadine alone and in the setting of maximum metabolic inhibition with ketoconazole. In the absence of metabolic inhibition, both drugs have a modest effect sub-10 milliseconds on the QTc. But in the setting of metabolic inhibition with ketoconazole one sees a tenfold increase in the effect size on QTc resulting in a mean increase of approximately 80 milliseconds with terfenadine. A pattern that is quite different from that seen with ranolazine.

It should also be emphasized that the preclinical profile of terfenadine is quite different from that of ranolazine and the drug's pro-arrhythmic potential is readily detected in preclinical models. This slide depicts for you the relationship between ranolazine plasma concentration and change in QTc for the entire population studied in red, as well as for a series of high risk subsets, including women, patients with heart failure, the elderly, patients with bradycardia and patients with coronary disease

compared with healthy volunteers.

And it is reassuring to note that the slope of this relationship is not different among these high risk subsets when compared with the general population. In addition to being reassuring, this is a profile that differs somewhat from a number of drugs known to cause torsade.

With regard to preclinical profile, it is important to underscore what you have heard already about the critical underpinnings of drug induced torsade, and that is the following triad. The prolongation of ventricular action potential resulting in QTc prolongation, one factor. Second and perhaps most important an increase in dispersion of refractoriness, which creates the substrate for reentry. And third the induction of early afterdepolarizations which may serve as a trigger for torsade.

As you have also heard, ranolazine does not induce early afterdepolarizations and it does not increase dispersion. It also does not cause arrhythmias in any of seven experimental models

tested. In contrast, ranolazine suppresses early afterdepolarizations and reverses both dispersion and ventricular arrhythmias caused by drugs that commonly cause torsade.

In summary, the QTc effects of ranolazine are well-characterized and linearly related to plasma concentration. However, adverse side effects primarily CNS and GI will, in a larger percentage of patients, limit exposures to concentrations in excess of 8000 nanograms per mL. Syncope does occur with ranolazine and is often viewed as a surrogate or a potential surrogate for ventricular arrhythmias. But among observed cases, there has been no evidence for an arrhythmic mechanism.

There has been no case of torsade observed in more than 1,700 patient-years of exposure and spontaneous ventricular arrhythmias are not more frequent on ranolazine than they are on placebo. And finally, an extensive nonclinical program demonstrates a unique electrophysiologic profile with no evidence of pro-arrhythmia.

In conclusion, ranolazine is an effective

and well-tolerated anti-anginal agent with a unique hemodynamically neutral clinical profile. The drug also has a unique preclinical profile in two respects. First, at least in my experience, this represents the most comprehensive preclinical assessment of any drug with an effect on cardiac repolarization. And second, the results of that comprehensive assessment provide a level of reassurance that has not previously been possible.

And that reassurance derives from the observations that despite the fact that ranolazine does prolong the QT interval, it does not increase transmural dispersion. It does not cause early afterdepolarizations. And it does not cause ventricular arrhythmias in any of seven animal models tested, including the most sensitive model, for the detection of drugs which cause torsade in humans.

Thus, we are left with a theoretical risk associated with a small degree of QTc prolongation. The combination of a unique and hemodynamically neutral clinical profile and a comprehensive and uniquely reassuring preclinical profile mitigates

strongly in favor of the management of this small theoretical risk by a combination of strategies, including dose titration, appropriate labeling, physician and patient education and post marketing studies to which the sponsor is committed. Thank you.

CHAIRMAN BORER: Thank you very much, Jeremy. Is there any further formal presentation?

DR. RUSKIN: No.

CHAIRMAN BORER: Okay. We'll take some time for questions now. I would like a clarification of the data before we begin that. Please, Dr. Belardinelli, you gave a very impressive, I thought, presentation. I'm wondering though if I understood your data correctly, none of the animal studies explored the possible effects of drug disease interaction as a substrate or an arrhythmogenic effect of this drug. Now, none of these animals had induced ischemia, I don't think. Is that right or is that not?

DR. BELARDINELLI: No, we did. Ranolazine has been a study in animal models with ischemia reperfusion and also in isolated perfused hearts. And

ranolazine actually decreases the incidents of ventricular fibrillation in these models at a concentration started at 1 micromolar and up to 10 micromolar.

CHAIRMAN BORER: Can you show us some of those data, please?

DR. BELARDINELLI: Yes. Let me start, okay, here we go. We have here, this actually was a study done awhile ago while this drug was at Syntex. And what is shown here is the incidence of ventricular fibrillation in a model of ischemia/reperfusion in rat isolated working heart. As you can see here, ranolazine at 100 nanomolar decreased the incidents by about 25 percent and about 36, 37 percent at 1 in 10 micromolar.

DR. THROCKMORTON: Sorry. Dr. Belardinelli, just a question. Does the rat have IKr?

DR. BELARDINELLI: The rat, if you produce an IKr blocker, will prolong the action potential. On the other hand, I should point it out that IKr, I don't know of any evidence that IKr would promote EF.

DR. THROCKMORTON: I take that as a no.

DR. BELARDINELLI: Actually, an IKr blocker would decrease reentry by prolonging the action potential.

DR. THROCKMORTON: Yes, and sorry, I was just asking a mechanism-based sort of question. I wasn't sure exactly what this model would inform if we didn't have IKr present.

DR. BELARDINELLI: And by the way, these that are here, the designs of the heart, that's also data in anesthetized animals as well.

CHAIRMAN BORER: Do you have similar data in other models with intact animals?

DR. BELARDINELLI: Okay. Can we go back to the previous slide? The one that we have all the different conditions where we tested ranolazine. Okay. I have listed here, Dr. Borer, eight well-accepted risk factors or principles and conditions for torsade de Pointes. We have tested ranolazine in almost all of these conditions, and we have provided reports in almost all of them. There is a few exceptions.

We did study the ranolazine and I want to

point it out, Item 5. We did a number of studies which I didn't show in my formal presentation to you where we attempted what I think is the ultimate test for this is to simulate ion channel mutation, a sodium channel ion mutation, and then we add drugs on top, I add ranolazine on top of that situation and we showed actually ranolazine actually suppressed arrhythmias caused under those conditions.

As far as other diseases since you alluded, number 6, is heart failure, which probably would be most people's concern, we have reported a study in which human ventricular myocytes from explanted hearts, terminal heart failure, this is done by Dr. Stanley Nattel, and in this study Dr. Nattel also failed to induce EADs. Although, he did prolong the action potential by about 12 to 13 percent. So we have vigorously pursued to find a situation where we could find a signal with ranolazine and results are here are no, no and no. We cannot find a signal with this agent that would produce a pro-arrhythmic signal that we mentioned earlier, EADs or increased transmural dispersion.

CHAIRMAN BORER: Okay. I think these are all very impressive and interesting. I think probably what most people would be interested in is the interaction with ischemia, though, because that's what you want to give them.

DR. BELARDINELLI: Yes. Ischemia is listed here.

CHAIRMAN BORER: Right. And what we've heard about is a rat model.

DR. BELARDINELLI: Yes.

CHAIRMAN BORER: An isolated perfused heart.

DR. BELARDINELLI: Correct.

CHAIRMAN BORER: Rat model that doesn't have IKr. Now, do we have other data?

DR. WOLFF: It might be useful to look at the occurrence of arrhythmias during ischemia induced by exercise during clinical testing, and we have those data displayed here. And you can see, and we didn't subject these to statistical analysis, but the occurrence of ventricular arrhythmias during both exercise and then during recovery was actually

trending downward with dose with ranolazine in pivotal trials.

DR. BELARDINELLI: Dr. Borer, to address your question, as I mentioned, we do have study of ranolazine in rat, anesthetized rat, LAD ligation followed by reperfusion. And again, ranolazine decreased induction EF, decreased the frequency of ventricular tachycardia. This data, unfortunately, has not been reported to the FDA.

CHAIRMAN BORER: I would be interested just to -- Doug, did you want to make a point here first?

DR. THROCKMORTON: Yes. I mean, Dr. Belardinelli, elegant presentation. Thank you for presenting an overview of the data from the sponsor's conclusions here. It's probably just worth noting that the FDA reviewers contested some aspects of the interpretation that you've presented today and just informed us, in fact, that the reviewers did conclude that there was evidence of transmural dispersion under conditions of hypokalemia. I understand that you and they have had an opportunity to talk about that and

disagree with that interpretation. But low, and now we're talking about 2 millimolar potassium concentration evaluation.

I guess, Charlie, you did those experiments. You may want to stand up and talk about it. But under those conditions, we believe we did -- there was evidence both from TPT and other sorts of things as well as transmural dispersion for -- under other evaluations for evidence for transmural dispersion. And so I just wanted to leave that with the audience to make sure that there was -- if we needed to have a conversation, we could.

DR. BELARDINELLI: I think I did show a slide. Maybe we should go back to the slide of core presentation and we can see what are the observations. But also, I think it is important to point it out that 2 millimolar, and I think all of you would agree with me, is an extreme condition. 2 millimolar potassium by itself is pro-arrhythmic. It would increase ventricular ectopy. And under even these extreme conditions, ranolazine, Dr. Antzelevitch was not able to see any arrhythmias in this preparation.

So we are very reassured that even under extreme condition of 2 millimolar, we didn't see any arrhythmogenic activity and this is the issue, I think, that we're arguing here or discussing is that a 2 millimolar, that's this small, increase that you see here from 16, 28 back to 15 and back to 35. It's important to know that in no occasion these numbers here went above 40 milliseconds, and in no occasion they approach the 90 or 80 milliseconds that is the threshold that Dr. Charlie Antzelevitch has demonstrated to be necessary to induce torsade. Charlie?

DR. ANTZELEVITCH: Thank you, Luiz. Charlie Antzelevitch, Masonic Medical Research Laboratory. Maybe I should preface my remarks by saying that we've had a revolution I think in our understanding and also in the methodologies that we have available for assessing QT prolonging drugs. And these are models that we have available today that are able to detect drugs that produce torsade de Pointes that have been problematic drugs, such as cisapride and terfenadine and most recently mibefradil have been

identified as causing torsade, and these are all drugs that have recently been withdrawn from the market.

Ranolazine is all of the models that have been tested and all of the stresses that it has been subjected to has failed to produce an arrhythmogenic signal. And this is one of them. If we could see that slide once more, 2 millimolar. Okay. Thank you. 2 millimolar potassium is a concentration that really presents the ultimate test of any drug, even a drug like verapamil that we know to be very safe will produce transmural dispersion, very serious transmural dispersion under these conditions. Yet, ranolazine fails to do so.

One of the interesting facets with respect to this slide is that this concentration of potassium reduces the space constance, so that electrotonic interaction is facilitated and transmural dispersion is reduced dramatically on the baseline conditions. And what the drug does, in fact, is just bring this up just a bit, but we're still well within the normal range.

DR. THROCKMORTON: Charlie, help me

remember. You had to go to 2 millimolar potassium to see terfenadine's effect. Is that correct?

DR. ANTZELEVITCH: With terfenadine, we were able to see it at 4 millimolar as well as 3 millimolar. I don't believe we ever tested it at 2.

DR. THROCKMORTON: Okay. All right.

DR. TEMPLE: But it wasn't the sort of stand-up that hit you in the face kind of thing, right? I mean, it needed to be pushed?

DR. ANTZELEVITCH: Yes, with terfenadine and we found the same to be true with mibefradil, that long exposures are necessary in order to unmask the arrhythmogenic actions of the drug.

DR. TEMPLE: Of course, that's not true clinically for terfenadine. You see it right away. If you get its concentration up to where it's at.

DR. ANTZELEVITCH: Right. It's a matter of loading the cell with the drug. And time is a function that allows you to load the cell.

DR. THROCKMORTON: Charlie, one other thing about these data. You didn't show it, but you had obviously done a whole graph, whole series of

other measures in this particular experiment TPT and APD 50s and 90s in the M cell region as well as the epicardium, although showed a consistent dose-response that, again this is 2 mL or more of potassium, again that didn't give you any pause, I guess?

DR. ANTZELEVITCH: No, it did not, because we are within the normal range. As Dr. Belardinelli indicated, TDR never exceeded 40 milliseconds. In the arterially perfused wedge preparation from the dog, the threshold is 90 milliseconds for the induction of reentry and the induction of torsade.

DR. THROCKMORTON: And tell me how many compounds that, it sounds like might lie in the sand, this is based on?

DR. ANTZELEVITCH: In fact, the slide enumerates the compounds that have been tested in these various models, and if we focus just on two columns, this column that indicates whether torsade de Pointes has been reported in the clinic with this particular drug and the other is the transmural dispersion of repolarization that has been noted with these experimental models. You'll note that in every

case in which torsade has been reported in the clinic, there is an increase in transmural dispersion of repolarization. When transmural dispersion has not been detected in the models, there is no indication or report of TdP. The only exception being amiodarone.

If we could have the next slide, please? So that more recently, we have calculated the sensitivity and the specificity of these models and the sensitivity being 90 percent and the specificity being 100 percent, and the sensitivity is limited only by the amiodarone experience, which, I think, we all recognize is a far lower incidence of torsade than we're used to seeing with other QT prolonging drugs.

DR. TEMPLE: Could you go back to the previous slide? It's very hard to read. Which are the drugs that prolong QT that are not a problem, other -- leaving aside amiodarone? I just can't see the names there.

DR. ANTZELEVITCH: Quinidine in high concentrations, verapamil.

DR. TEMPLE: Verapamil, you're counting verapamil as prolonging the QT?

DR. ANTZELEVITCH: Verapamil normally does not, but under hypokalemia conditions will prolong QT.

DR. TEMPLE: Okay. So that's a little iffy. What are the others?

DR. ANTZELEVITCH: Sodium pentobarbital.

DR. TEMPLE: Yes, well.

DR. ANTZELEVITCH: IKs block and the presence of beta blockers and the final one is ranolazine.

DR. TEMPLE: Okay. But that's not a whole lot of drugs that prolong the QT by a meaningful amount and that don't cause dispersion and turn out to be clean. I mean, how many were there? Quinidine at high doses and mibefradil? No, mibefradil does, you said.

DR. ANTZELEVITCH: Yes.

DR. TEMPLE: We actually have that.

DR. ANTZELEVITCH: We have nine drugs and conditions that prolong TDR and have been reported to produce TdP.

DR. TEMPLE: Right. But they also prolong the QT. I was interested in the ones -- I mean, the

case you are making for ranolazine is sure it prolongs the QT, but it doesn't do this other bad thing that causes problems. And how many drugs help make that case in the negative way, that is they prolong the QT, but they don't cause repolarization and therefore we have reason to hope that ranolazine wouldn't.

DR. ANTZELEVITCH: Right.

DR. TEMPLE: I mean, I don't know what to make of pentobarbital. I'm not sure anybody uses it much any more, but there are not a lot of members in that set, are there?

DR. ANTZELEVITCH: I agree. If we could go to AN8?

DR. THROCKMORTON: Now, wait a minute. Before you go, so moxifloxacin you are asserting now increases dispersion and supported to cause torsade so that I guess the dispersion part I wasn't familiar with.

DR. ANTZELEVITCH: Okay. If we could to go -- before we go to AN8, if we could go to AN3? Thank you. This is the dose-response effect of moxifloxacin in isolated epicardium and M cell

preparations showing that there is a remarkable effect of the drug, particularly at high doses, to prolong the action potential of the M cell, but not that of epicardium, such that this is the dose-response relationship in the M cell and epicardium.

And as a consequence, we see a dramatic increase in transmural dispersion of repolarization. And this occurs at concentrations of moxifloxacin that are 1 to 2 orders magnitude above the therapeutic range. But yet, it's sensitive enough to pick up a drug that perhaps produces torsade in one in a million cases, that's the estimate today.

DR. THROCKMORTON: Right. Okay. The lower right hand panel is what you're talking about now, Charlie. The control, if I see -- am I reading those very small letters over there right? The control is 100?

DR. ANTZELEVITCH: That's correct. These are isolated tissues.

DR. THROCKMORTON: Right. No, I understand the difficulties.

DR. ANTZELEVITCH: Yes.

DR. THROCKMORTON: I'm just back to the 90 sand line.

DR. ANTZELEVITCH: No.

DR. THROCKMORTON: That you had said earlier and I guess it's hard to have a line. I mean, you're right. Isolated tissue, it's got to be hard to do those kinds of things.

DR. ANTZELEVITCH: Right. The threshold is different in isolated tissues than it is in the wedge. Because here the tissues are not electrotonically connected to each other.

DR. TEMPLE: But you're really saying that moxi, if you could test such a thing, would be torsadogenic at a rate of one in a million. You don't think you know that yet, do you? I mean, I don't even know what the background rate for torsade is or would be.

DR. ANTZELEVITCH: We've begun to do those experiments in the wedge preparation, and we have one occurrence of torsade.

DR. BELARDINELLI: I just want a moment to expand a little bit on what Dr. Antzelevitch presented

to you.

MEMBER LORELL: That's interesting.

DR. BELARDINELLI: First of all, our conclusion that we will not expect ranolazine to cause torsade is not solely based on the work done on the wedge preparation that you heard very elegantly by Dr. Antzelevitch, include other preparations. Second point that I want to make to you is for every condition that Charlie has used to induce torsade with terfenadine and others the long exposures he tested equally with ranolazine.

I think what we can safely say is that the axis that we use in their totality, left ventricular wedge, the rabbit female isolated heart, and I should point it out that in rabbit female heart, Dr. Luc Hondeghem from Belgium published in March of this year that terfenadine causes EADs and causes ventricular tachycardia in 13 percent of the hearts and cisapride was in 80 percent of the hearts. We use exactly the same model and conditions used by Dr. Hondeghem.

So I think it's safe to say, therefore, that the sensitivity of the methods, the axis and

conditions that we use, that I readily use for this test, our axis are sensitive enough that they would have detected the pro-arrhythmic signals of agents such as you heard here, cisapride, moxifloxacin, terfenadine. No matter how difficult it is to induce these arrhythmic signals with these other agents.

DR. TEMPLE: Jeffrey, just one thing. Nobody I know thinks that ranolazine is terfenadine, which, you know, causes a rate as high as anything if you inhibit its metabolism. Nobody thinks that. The question is whether it is at some lower level of risk that is still real. And I don't know what to make of the moxi data. We're not sure there are any human cases. There are some that are up for debate. So I don't know what to make of that.

And the thing we've all been struck by, we actually have somebody working on this, is that it's not easy to find out what all of the known human torsadogens do with respect to all of these things. We're not bad on some of the newer ones, but we don't really know much about some of the older ones. And this may all be absolutely true, but there's not a lot

of human examples to base it on it seems to me. I mean, it's a lot about cisapride and terfenadine and that could be considered reassuring. I don't know what to make of mibefradil, which we never thought was torsadogenic anyway. So there's a fair amount of ambiguities. I'm sure the future will lay all this out in a perfect way. A question for everybody to think about is whether we know that yet.

CHAIRMAN BORER: Can I ask, you know, I take it that no one who has studied this drug believes that there is an important potential interaction between drug and disease, that is ischemic disease, that might be arrhythmogenic in an important way. Before we let it go, I would like to hear from Peter or Jeremy or anyone of your consultants who deal with this clinically about why you believe that there isn't an important interaction in Craig Pratt Study, which was, you know, a seminal study in the late '80s, alerted us to the importance of the drug disease interaction when ischemia becomes acute. So I would like to know why we believe on the basis of the data we have preclinical or clinical that there is no

important drug disease interaction here.

DR. KOWEY: Jeff, it's a very tough question, obviously, because the models that we use for the detection of the event that we're all most concerned about, which obviously is torsade, does not necessarily take into account ischemia. And, in fact, the truth of the matter is I'm not aware of any database in which that has been comprehensively studied. There is a piece of clinical data that you might find interesting that Andy will describe that has to do with the slope of QT and volunteers versus patients with ischemic heart disease. Andy, did you want to share that information? That might help you a bit, Jeff.

DR. WOLFF: In the Population QTc Analysis, the slope of the relationship between the changing QTc and the ranolazine plasma concentration was the same in the healthy volunteers as it was in the patients who had severe ischemic heart disease as exercise testing showed. And then the other piece of information, I think, we've already look at was we just didn't see an increase in the incidence of

exercise induced arrhythmias when we were creating ischemia in these patients and, in fact, it went in the other direction.

UNIDENTIFIED SPEAKER: What about that slide?

CHAIRMAN BORER: You know, if it's Slide CR-9 that you're referring to, those slopes sort of look sort of like they are the same, but they are not really the same. A CAD subgroup actually I couldn't see, because it was underneath the red line at the top.

DR. WOLFF: Well, no, it's actually underneath the white line for that.

CHAIRMAN BORER: Oh, then I really couldn't see it.

DR. WOLFF: Yes. So actually the patients greater than the age of 65 and with CAD actually have a slope that's somewhat lower than those overall.

CHAIRMAN BORER: Okay.

MEMBER NISSEN: So let me just follow on that a little bit with CS-5. Okay. And go ahead and put those limits on there. And, you know, I was

struck by this, obviously, that even when you force levels to very high levels, nobody goes more than 60 milliseconds above baseline. Is that right? Okay. Now, let's look at CS-8. So these are normal volunteers, are they not?

DR. WOLFF: Correct.

MEMBER NISSEN: Yes, these are not patients. Now, let's look at CS-8 and we see that there are patients in the patient population that do go, you know, 14 in a thousand or 6 patients at 1,500. So in terms of the outlier analysis, it looks like there is a difference here. That in the normal volunteers, you can push this dose to the level of toxicity and you can't get QTc to go up by more than 60 milliseconds, but you can get it at therapeutic concentrations.

DR. WOLFF: Well, I think that what's important here that is not on the slide is the number of ECGs that this reflects and the duration of exposure and time, so that, you know, the data on placebo come just from the MARISA and CARISA placebo periods. The data on the other doses, excluding

1,500, which isn't allowed in open-label treatment, are a combination of the controlled data and the open-label data. And so when we look at these outliers, we see outlier values not outlier patients.

You know, there is an occasional extreme value as you noticed from the 3111 data plot, even on placebo. There is a range of change from, you know, decreases to increases of around 16 milliseconds. So the measurement oscillates quite a lot even under normal conditions. And so over time, you know, patients will hit an outlier value, either an outlier change or an outlier absolute value, but no patient has ever had the majority of their ECGs be an outlier. And, in fact, the majority of patients who had had ever an outlier had one single outlier value out of all their ECGs.

UNIDENTIFIED SPEAKER: That's a good point.

CHAIRMAN BORER: Okay. Peter, is that the conclusion of your response?

DR. KOWEY: I think Jeremy.

DR. RUSKIN: May I add a comment, Jeff?

CHAIRMAN BORER: Yes, please.

DR. RUSKIN: To this question about the potential for a drug interaction here?

CHAIRMAN BORER: Please, do.

DR. RUSKIN: Because I think it's an important question and very difficult to answer. I just wanted to add one potential comment and that is that there is from a mechanistic standpoint, this would not be a class of drug in which you would expect an interaction with ischemia. For example, IKr blockers like d-sotalol are used routinely in the setting of ischemia and are safe. And even a drug like dofetilide, which is a potent IKr blocker and known to cause torsade, has a neutral mortality effect when studied in a post MI population.

The drugs that have been clearly proven to be dangerous are the sodium channel blockers, whose ECG signature is QRS prolongation. And there is no signal, based on the profile of this drug, that would put it into that category, and that's about as close as one can get, I think, to addressing that question.

CHAIRMAN BORER: Is that true despite that

fact that if I remember correctly this does block sodium channel as well as potassium channel or have I misunderstood?

DR. RUSKIN: The late sodium channel, but doesn't affect the upstroke. It doesn't affect the fast inward sodium current.

DR. BELARDINELLI: Correct. Ranolazine is a quite selective late INa inhibitor has little effect on peak INa in concentrations to produce, decrease, to rate or rise with the actual potential which will give an indication of the peak INa. You have to go to 50 to 100 micromolar.

CHAIRMAN BORER: Jeremy, I'm remembering QRS prolonged widening, and I don't remember in what study, but it would have been a preclinical study, is my guess. I seem to remember QRS widening seen in one of the models.

UNIDENTIFIED SPEAKER: It's a tiny bit of inhibitor, INa.

DR. WOLFF: Yes, in MARISA and CARISA, the QRS interval, I mean, because we've -- especially in MARISA with the crossover design has such sensitivity,

it does increase slightly. It's less than 1 millisecond or at about 1 millisecond at 1500. I don't know if we have -- we do. We'll show it in a moment here.

DR. THROCKMORTON: And start with different from what you would see with the sodium channel.

DR. WOLFF: Yes. Okay. Let's project that. There you go. There is the data on that, on a QRS interval for MARISA and it actually, you know, is a matter of here, for example, at peak. This is 2 milliseconds. At trough, this is 0.6 milliseconds. It's not statistically significant at 1500. It's marginally significant at 1.3 milliseconds and then it is significant at 3 milliseconds.

DR. THROCKMORTON: You must have looked at that in the infusion study as well, which would have had less random collection of ECGs. Do you know what it showed there? I don't remember.

DR. WOLFF: I believe there were similar very small on the order of a millisecond change.

DR. THROCKMORTON: All right. So right.

There is an effect on the QRS. It seems very small. Well, I guess that would probably be the more appropriate way to characterize this effect rather than there is nothing here.

DR. WOLFF: Sure enough. But in order of magnitude below what you would see with the Class 1A or C drugs certainly.

CHAIRMAN BORER: Alan?

MEMBER HIRSCH: Well, just one more question regarding things that might potentiate this arrhythmia is I couldn't quite tell from the patient populations how many individuals had structural heart disease, known LV dilation, etcetera.

DR. WOLFF: We characterized the patients presence or absence of congestive heart failure clinically only. And so in the Phase 3 trials we excluded patients with Class 3 or 4 congestive heart failure. And so in the thousand plus patients in the Phase 3 clinical studies about a quarter of the patients had a history of congestive heart failure, but we didn't measure their ejection fractions or anything quantitative.

CHAIRMAN BORER: Ed, I was waiting for you to weigh in here.

DR. PRITCHETT: Yes, Andy, I want to go back to some of the clinical observations you made about syncope. And you implied, you know, I guess, I think, you know, to me syncope is loss of consciousness accompanied by loss of postural tone. You fall down because your head doesn't work. And in the infusion studies, syncope was reported. These were normal volunteers who were hooked up to an ECG machine lying down in bed with an IV running into them, and yet something happened that was reported at syncope. What on earth was that? I mean, what did the people who were there describe? Not what did it map to in a med return.

DR. WOLFF: No, I understand.

DR. PRITCHETT: What really went on there?

DR. WOLFF: I think my colleague, Dr. Markus Jerling, was primarily responsible for this trial, and so he was the one in direct contact with the investigators. I think he is in best position to describe just what you're asking.

DR. JERLING: Thank you. I'm Markus Jerling, clinical pharmacologist at CV Therapeutics. It is true that these patients had or subjects had in the continuous infusion, they had also continuous monitoring ongoing. We still attempted to take erect blood pressure. They still had to go to the bathroom. And every single thing occurred in the erect or the sitting position. And what typically happened was that they already had, I would say, quite manifest systems of nausea, but this was a study where both we and the side tried to push it a bit.

And a typical event can be when someone was then up for an erect blood pressure and then they develop this syncope as well. We had one index case actually where also we had a reduction in the vigilance and since it started to become known in the trial there was a neurologist onboard as well who confirmed that this was associated then with nystagmus and other CNS effects, so it seems to be a combination of CNS effect that this real high concentration and then the postural situation.

DR. PRITCHETT: And the ECG monitoring at

the time this occurred wasn't bradycardia? I mean, these patients, at the time this happened, were having vasovagal?

DR. JERLING: Yes, when they actually then developed the vasovagal, it wasn't the bradycardia, but immediately prior to that, no.

DR. PRITCHETT: No.

DR. JERLING: So you didn't typically see reduction in heart rate all the time, but it was when the very event occurred.

DR. PRITCHETT: Okay. Now, what about the patients? There were several patients in CARISA who were reported to have syncope. What was that? I mean, what do we know about those events? Andy, do you know?

DR. WOLFF: I think probably the most instructive overview of the 38 patients, who had syncope, can be made by Professor John Camm. He has had an opportunity to review all of them in some detail. And I think his opinion of what is going on is as instructive as we'll be able to get.

DR. CAMM: Dr. Borer, ladies and

gentlemen, John Camm from London in the U.K. I have had the opportunity at looking at the 38 patients who are reported in the ranolazine dossier. What I have been able to do is look at the narratives. The narratives are not always complete by any means and they are not totally instructive. But what I can say about it is that of the 38 patients, 15 occasions were clearly situational reflex orthostatic. And in two of the cases where there wasn't sufficient information to really judge that myself, at least the verbatim records suggested vasovagal reactions. So that is 17 out of 38 instances.

There were several instances in which syncope occurred against the background of an arrhythmia. In several instances, two I think, it was described as sinus node disease. It may well have been due to co-medications such as beta blockers and calcium antagonists and such like, but there is very little detail, other than the comment that the investigator felt that sinus node disease might be responsible. There were two instances in which there was a recording of ventricular arrhythmia.

In one case, syncope was said to occur and it was a non-serious event due to ventricular fibrillation, which the investigator felt was serious. It was in the setting of an acute coronary syndrome and quite clearly is an ischemic induced arrhythmia, not a polymorphic ventricular tachycardia like torsade. The second instance was a case where ventricular tachycardia occurred and this was related to an acute myocardial infarction which had occurred some five days previously. This was a monomorphic arrhythmia.

In both of those instances, there are electrocardiograms recorded either before or after the event, which clearly don't show any marked QT prolongation, so they don't seem to be torsade related arrhythmias. There was one instance in which a patient had syncope when he had atrial fibrillation, and the QT was measured at this time, and was reported as 521 milliseconds. In fact, this is the only instance where syncope occurred in someone with a QT interval over 500 milliseconds.

This patient was taking propafenone at the

time, and what part that played in the prolongation of the QT interval, I don't know. But when the patient was back in sinus rhythm and off the propafenone but still on the same dose of ranolazine, the QT interval was back in the normal range at 300-something milliseconds.

DR. PRITCHETT: Did you see the ECG of atrial fibrillation?

DR. CAMM: No, I didn't see the ECG. I have looked only at the narratives.

DR. PRITCHETT: I see.

DR. CAMM: So I didn't see the electrocardiogram, but there was a little bit more information. They said the patient had atrial fibrillation and atrial flutter. He was taking propafenone. My own feeling was it might well have been intermittent increase conduction to the ventricals that was causing this problem, but there wasn't a smack of torsade about that particular case. Now, those are the only cases where an arrhythmia is mentioned in the storyboard of these 38 patients.

Steve's question this morning about

glycerol trinitrate involved me looking back through the narratives during the break this morning to see exactly how many patients that might apply to. There were -- I found 14 patients of the 38 where glycerol trinitrate was listed in the co-medications, and you've already heard Andy Wolff's description of how many of them were taking other vasodilator compounds.

In only one instance is there a clear story that the patient took two puffs of glycerol trinitrate and within a minute or so had collapsed with a syncope event. There is another instance where a patient was wearing a nitroglycerin patch that might have contributed to the syncope as well, but that was a protocol violation. So there remains, of course, a number of cases where we have precious little information about what causes syncope. But looking at the dossier as a whole, the one thing that you don't get from it is the impression that QT prolongation non-sustained ventricular tachycardia torsade, etcetera, is part of the story. It just doesn't emerge at all.

DR. PRITCHETT: Okay. Can I ask another

question?

CHAIRMAN BORER: Yes.

DR. PRITCHETT: Something flew by about patients with hepatic disease and the slope of the concentration QT interval curve. Can we see those data again? I mean, it looked like a striking outlier.

DR. WOLFF: It is. The only population that we have identified that has a steeper slope than the others and it's about 7 milliseconds a thousand.

DR. PRITCHETT: Compared to 2.4.

DR. WOLFF: Compared with around 2.4 and everyone else.

DR. PRITCHETT: And can you elaborate on what you think is going on there? I mean, can you explain that based on the way those data were collected in those patients or the study?

DR. WOLFF: Well, I'm going to ask my colleague, Dr. Sam Lee, to come to the podium and talk about QT measurements in patients with clinically evident liver disease. But we do know that their QTs start out longer and we don't know of any other data

that we can find about the drug response to QT prolonging drugs and cirrhosis. This is what we found.

DR. PRITCHETT: Do you have the slide that has those data on it? Can you just put it up?

DR. WOLFF: This isn't the one I showed. Can we just show the slide form the core presentation, please? There we go.

DR. PRITCHETT: But just help me understand. The patients with hepatic impairment was that a special study that you did, you know, pharmacokinetics?

DR. WOLFF: Yes, it was.

DR. PRITCHETT: It was.

DR. WOLFF: Yes, it was.

DR. PRITCHETT: So those weren't patients out of CARISA, for instance?

DR. WOLFF: No, they weren't. These were patients with very clinically evidence hepatic disease, either mild or moderately impaired, and they all had signs and symptoms of obvious hepatic impairment. Dr. Jerling could actually describe those

occasions.

DR. PRITCHETT: Well, I mean, what was the study? I mean, the slope?

DR. WOLFF: The study was a study that was done to look at the pharmacokinetics of ranolazine in patients with hepatic impairment, which I think you know you would do in any drug development program for chronical therapy. And as we always did throughout the program, we collected frequent ECGs and had them read at a single core laboratory in order to try as best as we could to characterize this effect. And it is only when you put the hepatic patients into the population analysis, as the Agency did, that they fall out as a population with the separate slope of about 7 milliseconds per 1000 nanograms per mL.

So I think the observation we agree with, the meaning of it is a little tougher to sort out. As I said before, Dr. Lee will comment. Patients with cirrhosis have longer QTs, whether their response is more prominent to the effects of QT prolonging drugs, we're not able -- we searched the literature. We can't find any similar kind of study.

DR. LEE: I'm Dr. Sam Lee. May I have 411, please. I think it underscores that we know relatively little about how the heart functions in people with cirrhosis, but what we've discovered over the past 15 or so years is that despite a hyperdynamic circulation in increased cardiac output at baseline in patients with cirrhosis, they have a blunted systolic and diastolic contractile response to various stimuli and about almost half have a prolonged QT interval.

However, there has been no increased risk of torsade de Pointes, at least in the world literature up to now, in patients with cirrhosis in the absence of a known torsadogenic event, such as hypokalemia. And if the Committee wants to be bored, I'll be happy to elaborate on my research on mechanisms of this effect.

DR. PRITCHETT: I think that covers it on that capacity. What you have told me is what we know.

DR. CAMM: Thank you.

CHAIRMAN BORER: It is 12:05. We'll have a break now so that people who need to check out can do so. We're not going to take a formal lunch break.

We'll come back here at 12:30 and get started again. And at 1:00, we'll take a moment to ask for public comment and then we'll finish. We'll take the remainder of the afternoon to complete the evaluation with questions and the FDA advisory questions.

(Whereupon, the hearing was recessed at 12:06 p.m. to reconvene at 12:35 p.m. this same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

12:35 p.m.

CHAIRMAN BORER: Let's begin with the questions that we didn't handle before the break. There was one from Tom Pickering and one from Ron Portman and then maybe some others. Tom, why don't you start?

MEMBER PICKERING: Okay. I wanted to return to this question of the syncope. This morning we heard that it is not a drug that lowers blood pressure and yet the syncopal episodes, I think, are being attributed to postural hypotension, which in turn are being attributed to alpha-1 blockade. And I think you said that the incident is similar to that is seen in alpha-1 blockers. But alpha-1 blockers, in general, lower blood pressure in a predictable way and so, there seems to be some disconnect there if this is not an antihypertensive drug.

And one of the other things about alpha-1 blockers is that you get a first dose effect whereby you may get a very marked reduction after the first

dose that is not seen in subsequent doses. So, one question I would have is have you looked to see if there is a first dose effect and are you sure that the syncope is due to postural hypotension and vagal bradycardia?

Also, in the younger patients, I think, in Table 59, 58, I'm sorry, you report 11 cases of syncope in the young, healthy people, but by my reading only 5 of these were on what you might call mega doses with plasma levels above 2000 or on doses, oral doses above 1500. So, it looks as though it occurs within the proposed therapeutic range.

DR. WOLFF: If I could have this slide, please? Here you see the data from a Controlled Overdose Study, CVT 3111, and you see the incidence of nausea and vomiting in the pink bars, dizziness in the blue bars and then postural hypotension as the target plasma concentration by infusion was increased. And you can see there is a fairly clear dose related effect in these healthy volunteers.

On the next slide, this is from a study in which we were evaluating 1500 milligrams twice a day

and 2000 milligrams twice a day, and it really should be noted this is bid and it's steady-state. And you can see that as you get to the higher plasma levels, which here is around 7500 on 2000 milligrams twice a day, something over 5000 nanograms per mL at 1500, the orthostatic blood pressure change does increase or, in other words, there is a bigger change in orthostatic blood pressure upon standing.

The fact of the matter is these concentrations are well above where the therapeutic range is, which is, you know, more down here between around, let's say, 825 nanograms per mL. So when you look at the pharmacology data as well, you do begin to see the alpha-1 adrenergic blockade IC-50s occurring at concentrations that are here and above. So, the clinical observation really does fit with the preclinical pharmacology that at the lower end of the dose range we wouldn't expect to see any alpha-1 blockade. And as you go up to higher concentrations, you would then potentially see some effects consistent with alpha-1 blockade.

The reason why we don't see first dose

syncope, I believe, is because we've never given a first dose that is sufficiently large to get into the alpha blocking concentrations.

MEMBER PICKERING: But what about in the table, as I said, there are several subjects who appear to be not on large doses.

DR. WOLFF: Well, I think Professor Camm reviewed them. And can we see the table, please? The table that you're asking about.

MEMBER HIRSCH: Well, might you overlay the syncope out of the dose response that you had earlier?

DR. WOLFF: So, this is part of that table. I think as we get down to most of these 11 volunteers that had syncope had a very situational component to it. I think Professor Camm has spoken to them. You know, they are often with respect to defecation or urination and so forth and so on.

MEMBER PICKERING: There's another part to that table.

DR. WOLFF: Can we go forward? So, erect vital signs with a single dose of 342 milligrams, that

shouldn't have produced very high plasma concentration. So, they do appear in large part, as I have showed you on the first slide, to be related to dose and plasma concentration. It's also just not an uncommon event, and we have observed it at other concentrations. But, I think clearly the incidents do get higher as you go up on dose.

Here is another look at this issue. If we can have this slide, please? Okay. This is a Kaplan-Meier plot of syncope on 1500 milligrams twice a day, 1000 milligrams twice a day, and then placebo and 750 and 500 in the IR doses. And I think this shows part of why we don't want to use the 1500 milligram twice daily dose, and also why we recommend not starting at 1000 milligrams. If you are randomized to 1000 milligrams, we do see a very clear incidence of syncope that is less than on 1500 and separates away from the other doses.

So, if you think about the controlled clinical trials 5 cases of syncope occurred in CARISA in patients who were randomized directly to 1000. The other three were in patients who were, you know,

forced to 1500 as part of the study design. I believe this slide indicates that if you start dosing at a low dose as we presently propose and then titrate carefully out this, this is a problem that can largely be avoided.

MEMBER PICKERING: Do you have any blood pressure measurements if you start at 500 bid, you know, supine understanding blood pressures?

DR. WOLFF: Yes, we do. There is very little change at 500 milligrams twice a day in blood pressure, neither supine nor erect.

CHAIRMAN BORER: Ron?

MEMBER PORTMAN: Can we see Slide CR-5, please? What I note that is missing from these comorbidities is chronic kidney disease. There are about 14 million people with a GFR less than 60 in the country, and with all the electrolytes and hemodynamic problems that these patients have, this drug could have some potential benefit for them. So, my question is how many patients with CKD have you studied so far?

DR. WOLFF: I'm sorry, how many patients with?

MEMBER PORTMAN: With chronic kidney disease.

DR. WOLFF: The most definitive study was the Clinical Pharmacology Study which I'm going to ask my colleague, Dr. Markus Jerling, to describe. We didn't have a large number of patients with very significant renal disease in MARISA or CARISA, because, you know, they were excluded. But we do know that it is important to understand the kinetics and dynamics in those patients. And so Dr. Jerling will talk about what we learned there.

DR. JERLING: Yes, if we can start to look at the pharmacokinetics in the special PK Study, rural regression plot. So this was a pharmacokinetics study with mild, moderate, severe renal impairment and matched controls, according to the guidance by the Agency. And we were interested here in the steady-state kinetics of ranolazine as a function of GA4. And this is the outcome of the study. We see the oral clearance, which will then be inverse to the concentration you achieve at the specific dose, as a function on creatinine clearance.

The boundaries are as defined by the guidance. And we saw, more or less, linear reduction in oral clearance with a reduction in creatinine clearance in the study. And when calculating the difference between the boundary of moderate, severe up to normal, the increase in concentration is about 80 percent in this population. We actually looked in the MARISA and CARISA combined for renal function as predicted by the Cockcroft-Gault formula.

There weren't any specific measurements done in a more precise way. And there were patients down to the high 20s and the low 30s. Not very many, though, but that's a function of the patient population. So in the pharmacokinetic analysis we did in a combined way, a PK analysis. We actually did not find any relationship. The reason is most probably that the number of patients with more severe impairment were too few to pick it up. But I think it is fair to state that the reduction in clearance in patients was not more pronounced than what you see in this special study.

MEMBER PORTMAN: Is this data enough to be

able to give dosing guidelines for nephrologists who deal with these patients at the different degrees of renal impairment?

DR. JERLING: Yes, we believe so. This is conducted in terms of both design and number of the patients according to the guidance. And what we have said that when you read severe impairment, you should start with a lower dose and the dose range should also be lower.

MEMBER PORTMAN: And in the few patients in MARISA and CARISA that you did have, was there any difference in efficacy or safety issues in the CKD patients?

DR. JERLING: I can first talk to the population efficacy analysis. We did not include renal impairment as a factor. However, since concentration was the driving factor, if it would only be related to change in the concentration, then you would predict actually to get the more efficacy.

DR. WOLFF: And we don't have a special analysis of the adverse events divided by patients with some degree of renal impairment and not. Markus,

can you speak to the tolerability though in these patients in the special study?

DR. JERLING: Yes. The dose selected for this study was 500 milligrams bid with an initial dose of 875 just to reach a steady-state a bit faster. We selected a dose at the lower range, because we didn't, at the time, know to what extent it would be related. And the adverse event profile was, I would say, similar to what we have seen at 500 bid in other populations at similar concentrations.

One effect that fell out was a slight increase in creatinine by about 10 percent. We have conducted a special study and found that it seems to be related to the tubular secretion, an inhibition to the secretion of creatinine that was fully reversible.

MEMBER PORTMAN: Okay. That's interesting. One last question. What do we --

CHAIRMAN BORER: Hold on a second.

MEMBER PORTMAN: What do we know about this drug for patients on dialysis? Is it dialyzable? And its protein binding?

DR. JERLING: We have not conducted a

study on that. We did not include such patients in that particular study. Protein binding is around 60 percent. They test quite wide volume of distribution, so I would expect that dialysis would not be very efficient in this case.

CHAIRMAN BORER: Paul and then Doug.

MEMBER ARMSTRONG: Jeff, I would like to start off by complementing Dr. Wolff and his colleagues for a very lucid presentation of a very comprehensive data set. I want to go from the kidney to the liver, as I'm sure others will. I've seen and heard a lot about mild and moderate hepatic dysfunction, but I haven't seen those defined. So I would like you to just define those parameters. And I would like you to help me with, I can envisage using this drug if it were approved, and certainly using it in patients who would be on a statin with some degree of hepatic congestion and heart failure.

And the issue about the statin effect on the liver and hepatic congestion and then trying to apply your information to those types of patients would be helpful to hear some discussion around that

point.

DR. WOLFF: Well, I think to describe more specifically the clinical characteristics of the patients with mild and moderate hepatic impairment that we studied, I'm going to ask Dr. Jerling again, because he was responsible for that part of the program.

DR. JERLING: Yes. If I may receive the slide with the pharmacokinetic parameters from the hepatic study, please? So, we conducted a study fairly much the same design as the renal study, again according to the guidance by the Agency in patients with mild and moderate hepatic impairment, classified according to the Childe-Pugh classification. And the matched controls are included, as well. These are steady-state data also at the 500 bid dose.

And we see that patients with mild impairment had pretty much the same PK parameters as the controls. So it doesn't seem that mild impairment would really translate into a pharmacokinetic consequence. Patients with moderate impairment had an increase by approximately 80 percent in concentration,

and that is true both for peak concentrations and for UC. And given that ranolazine is almost completely metabolized, it's really compatible with the reduction in functional mass. Hepatic blood flow wouldn't really contribute very much. This is not a high excretion drug. Suggested reduction of functional mass would explain this finding.

MEMBER ARMSTRONG: How would I, as a clinician, identify mild hepatic impairment? What would you suggest to me in terms of using the drug in that definition?

DR. JERLING: I believe that's a perfect question for our expert, Dr. Lee, to respond to.

UNIDENTIFIED SPEAKER: These patients with clinical impairments.

DR. LEE: In this study, all these patients had clinically evident cirrhosis, so Child Pew A and B, I think, and certainly anybody in a Child Pew Class B would have either very obvious ascites, jaundice or encephalopathy, something fairly obvious that the mild impairment the Child Pew Class A it's undeniable that there will be a very few that have no

obvious clinical detectability, either by symptoms, physical exam or liver chemistry.

Now, these patients were obvious clinically, but in the "real world" there are going to be a few people pop up and I would only suggest that a careful history, standard liver chemistry panel and if any doubt, perhaps an ultrasound or maybe consultation with your friendly hepatologist might be the way to go. How did I know a person from Edmonton would give me a hard time? Sorry, private joke.

DR. WOLFF: I think the important point was that the patients in the trial had clinically evident hepatic disease. They didn't just have elevated transaminases or something like that. They had clear liver disease.

CHAIRMAN BORER: Doug?

DR. THROCKMORTON: I'll try to remember "friendly hepatologist" for labeling maybe. That sounds like that would be good. I had a question actually back a couple. One, Dr. Portman, the Agency looked at whether there was an interaction by creatinine clearance with QT. To ask a sort of

question that goes along with hepatic impairment, is there a by disease interaction there as well? And we didn't identify one, so, in a sense that is a good thing.

The second thing though is I want to pick up on is something Dr. Pickering said, which, I have to say, had not occurred, which is not uncommon from Dr. Pickering, there were some things I missed. Alpha blocker interactions. I mean, we talk about -- this is all the way back to syncope now, Dr. Wolff. We're talking about interaction that at some higher doses, there is syncope that is mediated by an alpha adrenergic sort of effect. I'm sure we don't have any information about concomitant use with other alpha blockers. I don't know.

DR. WOLFF: Actually, we do and actually, it was one of the more increased co-therapies among the 37 patients who had syncope on ranolazine. You can see that 2 percent of the patients overall were taking an alpha-1 blocker, but 14 percent of the patients who had syncope were. I mentioned these data before, but we can look at them now.

There was a rough, you know, doubling in the incidents in the patients who had syncope and the use of long-acting nitrates, of ACE inhibitors, of calcium channel blockers, including diltiazem. Maybe a slightly greater percentage of patients on beta blockers and diuretics. So drugs that are known to be associated with syncope were more commonly used in the patients who had syncope. And if we look at the distribution of the number of drugs among those patients --

CHAIRMAN BORER: Before you do that, what are those percentages? Are they percentages of the total number of people who fainted or the total number of people who were taking that drug?

DR. WOLFF: This means, for example, that 30 of 37 of the patients exposed to ranolazine who had syncope were taking nitrates for a percentage of 81 percent. And this, over here, would mean that 71 percent of the overall population. But nitrates is all nitrates, and so all the patients were taking sublingual nitroglycerin in the course of the trial. So these are column percentages based on the N up

here, and the N up here.

And then here is the distribution of the number of these different vasoactive medications that were being taken by the patients who experienced syncope. This one includes the one on placebo, as well, and you can see that about a third were taking two vasoactive medications, and then another third were taking three or more vasoactive medications. And if we just compare the incidence of syncope that we have observed on ranolazine to what is reported in the literature for other known alpha-1 or alpha-1 beta blockers, it's roughly comparable.

CHAIRMAN BORER: Okay. I'm going to open the meeting to public comment now for a moment, if there is any. For that purpose, let me read this guidance.

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Now, is there anyone here who wants to make a statement about the matters at hand today? If not, we'll proceed with the meeting. Steve?

MEMBER NISSEN: Okay. First of all, let me add to, I think, several people's comments that I thought that the presentation today was very lucid and

I really appreciated the care with which the sponsor prepared today. We got really a lot of information succinctly presented. It made our job a lot easier. So I don't have as many questions as I might have. In fact, the Committee actually asked many of them that I was going to ask, but I have a few.

I wonder if someone could tell me about 2D6 poor metabolizers. I know this compound is partially metabolized by 2D6 and we know that some portion of the population is 2D6 poor metabolizers. What do we know about those people?

DR. JERLING: Yes. We have conducted a long interaction study with paroxetine and that will highlight this, and as shown in what Dr. Wolff presented previously, the increase in concentrations of ranolazine was 23 percent. And we actually added another test in that study to confirm what happened. We didn't genotype, but what we did in the study was to phenotype in the dextromethorphan test. So it was done on three occasions. First, at baseline and these were healthy volunteers. Second, at steady-state ranolazine and third, at steady-state ranolazine plus

paroxetine. Paroxetine is a potent CYP2D6 inhibitor. For obvious reasons, we didn't select quinidine in this study.

And what we found was that there was a certain shift on ranolazine only, but not to the extent that anyone turned into poor metabolizer as defined by the phenotype. But when we added paroxetine, all but one became a poor metabolizer. And that means that the situation in this study would mimic a situation where you have a genotypically poor metabolizer, and then you saw an increase by 23 percent of the ranolazine concentrations.

MEMBER NISSEN: Okay. That's actually helpful. You mentioned that, obviously, you didn't do the study with quinidine, but it was a question actually, my next question on my list, which is to help you understand where, I think, many of us on the Committee are at is you have presented preclinical data that tend to be reassuring. The QT prolongation data tend to make us worry.

And so we want to explore as much as we can about what you know about what happens when you

give this drug along with other agents. And so, you know, patients with chronic coronary disease, some of them may be on anti-arrhythmic drugs. And so what I want to try to understand is: what happens, what happens if you give ranolazine to a patient that is on an anti-arrhythmic agent that might, in and of itself, have some effect on QTc?

DR. WOLFF: Well, with respect to Type 1 anti-arrhythmic agents, which I think would be what you're largely concerned about, we excluded them from the Phase 3 clinical trials, so we didn't really have the developed understanding of the cellular electrophysiology at the time we were beginning those trials that we now have due to the efforts of Dr. Belardinelli and his colleagues.

So we really don't have direct clinical experience, and then we would have to rely on the preclinical data. The preclinical data actually would suggest, for example, that somebody who had a very long QT on sotalol might experience shortening with ranolazine, but those data don't exist at this point. And so our proposed labeling currently would be to

caution against the use of one QT prolonging drug with ranolazine. I don't believe I have ever seen a study done with any two QT prolonging drugs together to understand what happens clinically.

MEMBER NISSEN: Well, but on the other hand, you have made the case here that the QT prolongation that ranolazine produces is not clinically important.

DR. WOLFF: That's our position. That is very different from what is seen with drugs that cause torsade.

MEMBER NISSEN: I mean, obviously, you know, we have to think about the population that's likely to get the drug and, you know, I must tell you that one of my obvious concerns is that when drugs get out in the general community, you know, even when you put things in the label, people have a tendency to give drugs together, anyway, and there are certainly a lot of people out there on drugs like quinidine.

And so, you know, it seems to me at least in some sense, it would be reassuring to know that there isn't some incredibly important interaction that

occurs when you give a patient with coronary heart disease an anti-arrhythmic drug along with ranolazine. But I take it that there is no data, so we can't really answer that question.

DR. TEMPLE: Steve, for other drugs that have been developed with modest QT prolonging, the labeling all says don't take any other drugs that prolong the QT interval. Whether that's remotely realistic or not, I don't know, but they all do say that.

MEMBER NISSEN: And nobody ever does, right?

DR. TEMPLE: But we really don't know. As he said, we don't know whether the effect is additive, superadditive, inhibitive. We just don't know.

MEMBER NISSEN: Right.

DR. TEMPLE: With any data we have ever seen.

MEMBER NISSEN: Okay. Fair enough. Just, you know, again in terms of my understanding of this, I needed to ask that question.

DR. TEMPLE: But there is no question that

the use of ranolazine would be very large if it could reverse the bad effects of dofetilide, sotalol and other drugs, which we could name.

MEMBER NISSEN: Yes.

DR. TEMPLE: It's worth --

MEMBER NISSEN: Yes.

DR. TEMPLE: Just a little advert, it's worth taking a look at that.

MEMBER NISSEN: It did actually occur to me. It also occurred to me that a drug that lowers the hemoglobin A1c by 1 percent might have some potential clinical utility, as well, but we won't go there.

DR. KOWEY: Steve?

MEMBER NISSEN: Yes.

DR. KOWEY: I'm sorry. Peter Kowey.

MEMBER NISSEN: Yes.

DR. KOWEY: It's even more complex, because what we also don't know is if you were to reverse some of the QT prolonging effects with ranolazine of a drug like dofetilide or sotalol, whether you would still preserve efficacy of those

drugs for the indication you were using them. So not only do you have to look at the safety side, you would also have to look at the efficacy side. So, it's a fairly daunting task, but not one that isn't interesting scientifically.

MEMBER NISSEN: Yes, and of clinical relevance. I mean, I think, you know, the chances that this drug would get out in general use, given the millions of people we heard have angina, and never have it be given to a patient that's also on some anti-arrhythmic drug, I mean, the chances are zero. I mean, somebody is going to get this drug who is on quinidine, and so my argument would be the more we know about that, the better off we are.

DR. THROCKMORTON: Yes. And just to follow on that, you will be asked sort of explicitly to sort of be ready to comment on things like that, but this might be a case, an argument might be made that this drug is behaving a little differently than the kinds of drugs that we have typically seen in the past, places where, as has been pointed, we have typically not seen interaction studies. Although,

there is a study ongoing as a part of a Phase 4 commitment to, in fact, look at an interaction with two drugs like this. Peter is smiling. I'm sure he'll be delighted.

DR. KOWEY: No, that's exactly what I was going to say.

DR. THROCKMORTON: But the issue here is you have another interaction. You have an interaction by disease that is unprecedented. As everyone said, we don't -- we haven't seen that before. We have seen an interaction with gender, with quinidine. An interaction by disease of this magnitude, maybe we haven't looked hard enough, something like that. It just hasn't been seen. I don't know what that does to your level of assuredness. Does that tip the balance for needing additional interaction studies in this case? And you will help us out with that a bit later on.

MEMBER NISSEN: I will indeed. You know, it's interesting. We heard about the term "friendly hepatologist" and actually, the term "friendly cardiologist" is actually an oxymoron.

UNIDENTIFIED SPEAKER: That's harsh.

MEMBER NISSEN: It's tough, but it's true. I also want to explore with you another area. I mean, I am very interested in understanding better the drug-drug interaction potentials here, and so I wonder if you could put up the slide. There is a nice slide that shows various doses of diltiazem and the sort of drug-drug interactions. You got a variety of drugs on that slide, and I think you know which one.

DR. WOLFF: From the core presentation?

MEMBER NISSEN: Yes, from the core presentation, exactly.

DR. WOLFF: Here we go.

MEMBER NISSEN: Okay. Now, you know, it's interesting, because you did some studies with, I think, diltiazem 180 milligrams. Wasn't that your comparitor in at least one of your --

DR. WOLFF: It was the background treatment.

MEMBER NISSEN: Yes.

DR. WOLFF: In CARISA.

MEMBER NISSEN: Yes, that's right. Okay.

But, you know, it's actually interesting and I would be interested in the other Panel members, but I see a lot of patients on 240 and 360 milligrams of diltiazem. Now, the 360 milligram dose of diltiazem increases. Is that peak concentration? Is that correct?

DR. WOLFF: I believe it is.

MEMBER NISSEN: Or AUC?

DR. WOLFF: Markus, can you?

MEMBER NISSEN: And what are the numbers on the right?

DR. WOLFF: These numbers are the fold increase compared to ranolazine as monotherapy.

MEMBER NISSEN: Yes, yes.

DR. TEMPLE: So they are the same numbers that are on the bottom, because they are not? I mean, look, push 1.5 up and it's not where -- and it's where 1.2 is.

MEMBER NISSEN: Within the limits of slide-making, I mean, Bob, gee, give them a break here. I mean, I actually know the people who are making the slides here. They are pretty good, you

know.

DR. TEMPLE: Well, it has been bothering me for a half hour.

MEMBER NISSEN: All right. Well, if I may pursue this a little bit. Okay. Now, the dose range that you are recommending here is 500 bid up to 1000 bid. Isn't that right?

DR. WOLFF: Except in patients receiving doses of diltiazem larger than or equal to 240 milligrams a day or doses of verapamil at 360.

MEMBER NISSEN: And what would you recommend for those?

DR. WOLFF: Starting at 375 and stopping at 750.

MEMBER NISSEN: I see. So the formulations you are going to make available are? What would be the formulations?

DR. WOLFF: Tablets of 375 milligrams and 500 milligrams.

MEMBER NISSEN: I see. So the idea then would be that 375 bid would be equivalent to 1000 bid in a patient not taking diltiazem. Am I with you? In

other words, if you take the AUC, approximately, you would expect to elevate serum levels to the level of about 1000 bid?

DR. WOLFF: Well, no. I mean, I think it would be something less than that. It would be around 750 bid. I mean, there is a rough -- depending on the dose of diltiazem that we're discussing, because the inhibition of 3A4 by diltiazem is dose related, but at 240 and 360 it's on the order of a doubling.

MEMBER NISSEN: Yes.

DR. WOLFF: So if you started at 375 bid, it would be like starting at 750 bid.

MEMBER NISSEN: Yes. I'm just a knuckle-dragging cardiologist, so I don't do math too well. But if you take, you know, 375 and multiply it by 2.4, don't you sort of get 1000 more or less? Isn't that about right?

DR. WOLFF: You're between 750 and 1000.

MEMBER NISSEN: Yes. Okay.

DR. WOLFF: 2.4, yes.

MEMBER NISSEN: All right. So again, with the dosing that's available for that patient that

comes in -- see, I am imagining how this drug is going to be used. Patient comes into my office. They are good, you know, goodly doses of diltiazem. I have maxed them out on diltiazem. They still have angina and I want to give them ranolazine. So what that means then is that if I give them 375 bid, they are going to get blood levels very quickly similar to what I might get from another patient that would get 1000 bid. Is that right?

DR. WOLFF: Definitely, there would be an overlap in the range.

MEMBER NISSEN: All right.

DR. THROCKMORTON: But, Steve, that's going to get more complicated. Remember this drug is very wide inter-subject variability. I mean, the exact serum concentrations for an individual, hard to draw from a mean value.

DR. WOLFF: Yes.

MEMBER NISSEN: No, but I'm trying to understand. What I'm trying to understand is that what is the potential for a patient on concomitant meds to quickly get out of range, to quickly get to a

level that might be potentially harmful, might produce syncope. You know, we heard that if you start them at high doses right away, they tend to go to ground. And so I'm trying to understand the potential for this drug-drug interaction to get patients into trouble.

DR. WOLFF: I think what I said is that if they are started on high doses right away and they are going to go to ground, they go earlier, but the incidence is still very, you know, pretty low. It's not like it's a high risk.

MEMBER NISSEN: Yes.

DR. WOLFF: But it could be avoided by starting at lower doses.

MEMBER NISSEN: Yes. But we obviously do have an important interaction here and we just, you know, have to make sure we understand that between a very commonly used anti-anginal agent, diltiazem, and this drug and that, obviously, is something that would obviously in labeling be dealt with, but yes.

CHAIRMAN BORER: Bob?

DR. TEMPLE: Jeff, tell me if this isn't the time to raise it, but one of the ways you protect

yourself against problems like that is to not use the highest dose you conceivably could. So, I don't know when the right time to talk about it is, but you are talking as if 1000 twice a day is the desirable dose, but that was indistinguishable from 750 in the largest trial you did. So, one question I wanted to ask, at some point, I don't know if it's the right time, is why did you pick 1000 twice a day instead of 750 twice a day, because with 750 you're further away from trouble, presumably, even if somebody took verapamil, diltiazem or any of those?

DR. WOLFF: I believe that we did acknowledge to the Agency in the letter that that's definitely something worth discussing, is to limit dosing to 750 bid as a maximum dose. We would be willing to consider that.

CHAIRMAN BORER: I don't think Bob was suggesting limiting the dose as a maximum, but as a starting dose.

DR. TEMPLE: No, no, I was suggesting limiting it as a maximum, just because there is not a lot of dose-response data, but what you have doesn't

give any indication that 750 is --

CHAIRMAN BORER: Okay.

DR. TEMPLE: -- inferior to 1000.

CHAIRMAN BORER: Yes.

DR. TEMPLE: That was studied directly in a trough.

CHAIRMAN BORER: Yes, we will get --

DR. TEMPLE: It was numerically slightly better.

CHAIRMAN BORER: I'm sure we will get to the dose-response issue and answering your specific question, so this is a very reasonable time to raise the point.

DR. TEMPLE: Yes.

MEMBER NISSEN: So your response to that is why not 750?

DR. WOLFF: Well, I think that it would be a reasonable consideration to stop dosing at 750 if one is concerned about avoiding higher plasma concentrations. I think that there will also then be a limitation in efficacy for some patients. 1000 milligrams twice daily was relatively well tolerated.

It's certainly comparable to other anti-anginal drugs. But it is true that syncope never occurred on 500 or 750 milligrams twice daily in the controlled trials. It's also true that it only occurred in patients randomized to 1000, as well.

MEMBER NISSEN: But Bob's question was well, there wasn't any greater efficacy at 1000, so why push the drug to the point of toxicity if you don't have to?

DR. WOLFF: I think it's a reasonable consideration. I think that in general, the efficacy at 1000 -- what we know is that the plasma concentration is a good determinant of efficacy and that the dose produces a dose relationship for plasma concentrations. So although, in the CARISA Study, we didn't see an apparent difference between 750 and 1000, across our broader experience, patients on 1000 will generally have a higher plasma concentration than patients on 750, and that would generally predict greater efficacy. So, there would be an efficacy limitation, I believe, in keeping some patients from being titrated to 1000.

CHAIRMAN BORER: All right.

DR. WOLFF: But it would come at the savings of a better safety profile for sure.

CHAIRMAN BORER: Yes. I think although, again, I don't want to prejudge the discussion that will follow. I think one of the issues that we will be raising is the adequacy of the dose-response data in terms of the overall package that we're seeing and what that implies in terms of label writing and what that implies in terms of defining a benefit to risk relationship. But you have presented to us, I think, all the dose-response information you have, so I don't think we need to belabor that, at this point, but we will be discussing it. Steve?

MEMBER NISSEN: I also wanted to pursue some other drug interaction issues and particularly, I was -- actually, it was helpful that slide you showed a few minutes ago, that the patients that had syncope were more likely to be on long-acting nitrates, but you had just so little data on long-acting nitrates. And, I guess this is more of a comment than a question, but maybe you would like to respond to it.

I find it troubling when you have a drug you're going to add to a therapeutic armamentarium that currently consists primarily of beta blockers, calcium channel blockers and nitrates. And you have given us a fair amount of data on what happens when you give ranolazine with calcium channel blockers and what happens when you give ranolazine with beta blockers, but you have given us almost no information about what happens when you give ranolazine with nitrates.

And since I know that an awful lot, if not the majority, of patients that get this agent will be on long-acting nitrates, I am left without an understanding. Are they going to have a lot more syncope? Are there going to be other interactions that we need to know about? So can you help me here at all in understanding the potential interaction both for AEs and for efficacy with concomitant nitrate administration?

DR. WOLFF: Well, the data that we have from the open-label trials are the longest and most experience we have with patients being treated with

long-acting nitrates, and there we don't see any signal that there is a difficulty in adding the long-acting nitrates to ranolazine, which is the way it always would have been done, because as they come out of the open-label study or the double-blind study, they start on ranolazine and then other medications are added in as necessary after they are titrated to the top dose. We don't have an indication there would be a problem there, nor did we see anything that was a pattern that raised concern in the use of short-acting nitrates, sublingual nitroglycerin, during the two pivotal studies.

So there was actually an abundant co-administration of nitrates during the controlled studies. We, of course, precluded that just before the exercise test, so it didn't confound those measurements. But in terms of safety of administering nitrates with ranolazine, we don't see a problem there. We just see less nitrate use, in fact.

MEMBER NISSEN: Yes. But there is another, of course, issue and that is on the efficacy side. I mean, it seems to me that there is a group of

patients that would be very attractive to treat with this agent and let me describe the patients, and maybe you can help me understand what we know about the drug in these patients.

Somebody that has had every effort made to revascularize. They have angioplasty or bypass surgery. They still have angina. They are put on beta blockers. They are put on calcium channel blockers and they are put on nitrates, so called triple therapy. That is certainly the majority of patients that I have in my practice that have chronic angina. They are as well treated as they can. And now, I have got a new class of drugs and I want to add that drug on top of maximal therapy for the refractory patient.

What do we know about what happens? Does it retain efficacy in patients on triple therapy? Does it have reduced efficacy? Is there anything you can tell me about what happens in that refractory patient population?

DR. WOLFF: We don't have any data specifically in patients that are non-revascularizable

and are treated with maximal medical therapy. What we have is some data that I presented earlier under conditions of maximal effective individual drugs where we do see the drug adding efficacy, but in a patient population as you described, we just don't have that data.

MEMBER NISSEN: What about a patient population that can't tolerate any other anti-anginal drug? Let me tell you why I'm going here, is that we know we have safety concerns, and so the uniqueness of the drug, its uniqueness and its ability to provide clinical benefit for patients would mitigate against any safety concerns. I mean, if I knew I had a drug that could help the patient who really has unacceptable angina and can't tolerate other drugs, that that patient would benefit would be very helpful to me to know that those people can be benefitted by this class of agent. And it might make me lower my safety, you know, bar a little bit if I knew that. So can you help me with that?

DR. WOLFF: Well, these are the best data that we have going in that direction. I mean, we

haven't selected patients having identified them as being unable to tolerate any of the other anti-anginal medications. That hasn't been done, nor have we selected patients who have been previously revascularized or are unrevascularizable and who are on maximal medical therapy.

We do have patients that we have discussed earlier that would be difficult in whom to titrate up hemodynamically acting anti-anginal drugs, because they already have low blood pressures or slow heart rates or long PR intervals, and you see the drug working, you know, generally as well on them as it does in the others. And we have talked about the data in patients with heart failure who sometimes can be difficult to treat with some of the current agents and diabetes, reactive airways disease and any of the above.

The patients were not selected on the basis of their intolerance, but they all do have one thing or another that does cause problems, often, with tolerating current therapy, and we do see that the effect of the drug is maintained in the sub-population

of interest, as well as in those who don't fit into that sub-population.

MEMBER NISSEN: Yes. Okay. I mean, I think you have shown me what you can on that.

DR. WOLFF: I think that's what there is. Yes, sir.

MEMBER NISSEN: Yes. Okay. Now, can we see the data on the sudden deaths? So, you showed a slide that had the placebo and the treated patients for sudden death.

DR. WOLFF: Yes, from the core presentation.

MEMBER NISSEN: From the core presentation.

DR. WOLFF: The first slide on mortality. So, here on the top, we looked at events that were termed as sudden death or where the cause of death was listed as ventricular fibrillation or tachycardia or cardiac arrest. There were 23 of them, two on placebo, 21 on ranolazine. Again, one of the things that makes interpretation of all our safety data problematic is that the duration of follow-up on

placebo is less than a tenth of the experience on ranolazine.

The point estimates for sudden death are very similar, numerically slightly lower on ranolazine, but probably the most valid thing to say is that the 95 percent confidence interval about this estimate fits entirely within the 95 percent confidence about the placebo estimate.

MEMBER NISSEN: Yes. I was actually more interested here in sort of looking at all-cause mortality, because you have a little more data to work with there. Here is the issue. You know, we obviously have a drug that has some potential for adverse effects that may, at least, potentially be lethal. And so what we have is just no power here. I mean, I think -- would you agree that there is virtually no power to try to see a signal?

But I was troubled when I reviewed all of this that numerically, you know, cardiovascular death and all-cause mortality was higher with confidence intervals that are incredibly wide. And the question is, you know, is this reassuring, not reassuring or is

it simply no information at all? I would tend to take the position as really no information at all. There just isn't enough exposure comparatively between the placebo and ranolazine to know if there is any effect on all-cause mortality.

DR. WOLFF: Well, the data are few, but the duration problem at least can be addressed by going to the next slide and looking at controlled data. Now, admittedly, that reduces the ranolazine experience even further, because then there are no data from the long-term open-label follow-up. But at least you're looking at similar periods of risk for the placebo patients and the ranolazine treatment, and there you see actually on ranolazine SR and in CARISA, the numeric rate of mortality is actually lower on ranolazine compared to placebo. It's very similar when IR studies are added in. But again, the confidence intervals are wide and they are completely contained on the ranolazine side within the interval on the placebo side.

MEMBER NISSEN: Yes, with numbers --

DR. WOLFF: So there are few data.

MEMBER NISSEN: Yes, with numbers of three and four and seven. So, there really isn't anything here that can either reassure us or not reassure us about the effect of ranolazine on survival in these patients?

DR. WOLFF: The data are few, yes.

MEMBER NISSEN: They are few. Okay. You know, I think that was my reading, as well, and I wanted to make sure, you know, that we all agreed.

CHAIRMAN BORER: Can I ask you to go back to the previous slide for one second? I want to understand completely what that final column is telling us. What is the interval over which the incidence is defined? Is it per year or is it for total follow-up?

DR. WOLFF: This is per patient-year.

CHAIRMAN BORER: Per patient-year? Okay.

DR. WOLFF: Yes, it is.

CHAIRMAN BORER: Thank you.

MEMBER NISSEN: Okay. I think that's all the questions I have, Jeff.

CHAIRMAN BORER: Are there any other

questions? Paul?

MEMBER ARMSTRONG: We have heard a little bit about hypokalemia. The coexistence of hypomagnesemia and hypokalemia are pretty powerful substrate for ventricular arrhythmia in patients with coronary disease. Any comments about the coexistence of those two metabolic abnormalities commonly as a function of diuretic therapy and likelihood of problems?

DR. WOLFF: Yes. We looked at patients receiving potassium-wasting diuretics in the population analysis of concentration versus QT change, and the patients taking diuretics had the same slope of the relationship as did the other patients. There wasn't that much variability in the plasma or serum potassium concentrations, as you might imagine, in the controlled trials, so that seemed like a better way to do it and that's our best data to that point.

MEMBER ARMSTRONG: A second question is, as you know, there is concern about the coexistent use of Viagra and nitrates. Any exposure to Viagra in the patient population on ranolazine?

DR. WOLFF: Do we have any data from the long-term open-label studies with patients that received sildenafil? No, we don't.

CHAIRMAN BORER: Blase and then Steve and Bob?

MEMBER CARABELLO: One of the assertions is that the agent prevents angina without a change in heart rate, blood pressure or contractility, and I saw the blood pressure and heart rate data, but I haven't seen the contractility data.

DR. WOLFF: I think the best data that we have to speak to the effects of ranolazine on contractility are preclinical data, and I think that I will ask Dr. Belardinelli to come and present them.

DR. BELARDINELLI: The best piece of data we have, Dr. Carabello, with ranolazine and contractility is a study done actually not too long ago, and I have a slide here that I would like to show to you. This was done in Dr. Thomas Hintze's laboratory using awake dogs, instrument for measurement of heart rate, blood pressure, coronary blood flow and, as you see here, left ventricular

systolic pressure and dP/dt.

And these animals were exposed to ranolazine at concentration of 1, 3, 14 micromolar and 18 micromolar and measurements were made at various times during a steady-state of this concentration. As you can see here, there is very little things for me to report to you, because there is not much decrease, except at 18. It's about, I think, if my memory doesn't fail me, this is about a 10 percent reduction on the LV dP/dt. And furthermore, we have also done a study in isolated tissues. This is the rat left atria and, again, ranolazine did not decrease, did not produce any negative inotropic effect.

MEMBER CARABELLO: Actually, since you mentioned it, you said that Tom also looked at coronary blood flow.

DR. BELARDINELLI: Yes.

MEMBER CARABELLO: Do you happen to have those data?

DR. BELARDINELLI: Yes, we can show that slide, as well. Here we go. So, here is the lack of effect of ranolazine on coronary flow in the resting

dogs, either CBF or the resistance, coronary vascular resistance. So we haven't found any major effect of ranolazine on flow or contractility or dP/dt, I should say, in awake dogs.

MEMBER CARABELLO: Thank you.

CHAIRMAN BORER: Bob, and then we'll go back to Steve.

DR. TEMPLE: Just one thing about the last discussion. Correct me if I'm wrong. My impression was that if you don't see an increase now in the rate-pressure product, there is no basis for assuming that the mechanism is anything other than hemodynamic. That is, that it has some effect on blood pressure or heart rate during exercise, you might not see it at rest, and that that helps you because somehow you can get to the same rate-pressure product with a little extra exercise. So that is not evidence of a different mechanism.

But leaving that, I wanted to ask Steve the following question. If somebody wanted to claim that a drug has an additive effect to maximum doses of something else, there is no alternative that we could

see other than to study that and that is basically what our letter said. The other case you talked about, though, where you were looking at people who couldn't tolerate a beta blocker, say, because they got depressed on it or something like that or a CCB, because they had too much heart failure and no one wanted to use it or because they didn't like the edema, or whatever, would you need to study a drug that didn't seem to have those problems in that population in order to believe that it could be used in those populations?

That's my question or if you thought you did, how much do you have to? Because, isn't it sort of obvious that if it doesn't cause depression, it won't cause depression in people who get depressed on a beta blocker? Isn't it obvious that if it doesn't cause edema, it won't cause edema in people who have edema?

MEMBER NISSEN: You know, it's interesting, but we see patients that seem to have trouble tolerating almost any drug you give them. You know, they are sort of the "bad actors" and they drive

every physician absolutely crazy, because whatever you give them, something seems to happen. And, so, you do get some reassurance from the fact that there really is something different about this drug. If you take some people that, you know, can't tolerate a calcium channel blocker, can't tolerate a beta blocker, but they can tolerate this drug, then it could actually be used in that population.

And to me, that would be valuable, because it would tell me that if I have safety concerns and yet I have a drug that people who are pretty desperate for some relief could get relief from that drug, it would make me feel better about having that drug available.

DR. TEMPLE: Yes. What I'm asking is not whether that's true, because you said that before.

MEMBER NISSEN: Yes.

DR. TEMPLE: I understand.

MEMBER NISSEN: Yes.

DR. TEMPLE: But do you actually -- this may sound like an odd question coming from me. Do you actually have to study that or do you already know

from the studies in other people that it doesn't cause those things that cause intolerance to beta blockers, CCBs, because you have got all this data and it doesn't show those things?

MEMBER NISSEN: I think --

DR. TEMPLE: How much, you know, I don't know. There is a lot of questions. You could ask the same thing about cough and ACE inhibitors and stuff.

MEMBER NISSEN: Yes.

DR. TEMPLE: How much data do you need, if there is no evidence of cough, to know that it won't cause cough and the people who cough too much on the ACE inhibitor might be able to use this? Now, we have made people study that.

MEMBER NISSEN: Yes.

DR. TEMPLE: But still, it seems worth discussing.

MEMBER NISSEN: Yes.

DR. TEMPLE: Because it's a question of how much data you actually need.

MEMBER NISSEN: Yes.

DR. TEMPLE: To feel comfortable about

that question, which seems quite distinct to me from is there additive effectiveness in that setting, which I see no alternative but to study.

MEMBER NISSEN: Your question is very provocative and I would be interested in other panel members' thoughts about that, but to me, I'm always more comfortable when I have the data. You know, when the study has been done and, you know, when you know what happens, it just gives you some added confidence. And frankly, I think it gives the medical community added confidence. I mean, I think it tells us hey, look, here is a drug you can give to people that just can't tolerate anything else and you can help them. And so, I think it would be good marketing for a company to do such a study.

The question is is it a regulatory issue? Well, maybe it still is for me if there is some risk involved in convincing myself that the benefits that the therapy outweigh the potential risks to really actually know that that population would be benefitted. I think I would like to see the data.

CHAIRMAN BORER: Okay. Let me summarize

that answer. I will. I think everybody would be perfectly happy if a drug was shown to be effective, and we'll get to acceptably safe in a moment, to do the experiment of trying it in anyone with the relevant condition. The only limitation to attempting that experiment would be how much you have to pay for it in terms of safety. And the greater your concern, your safety concern, the greater the need to have more precise information about the likelihood of efficacy.

But that is not a specific answer with regard to what's needed with this drug, which we'll get to. I think in general, my own opinion is absent particular safety concerns, if the drug is effective, you can perform the experiment in an individual patient after the drug is approved. Beverly?

MEMBER LORELL: Mr. Chairman, could I move to pick up on an issue that was discussed a little earlier this afternoon, and that is the alpha blockade issue, and it relates a bit to the issues that you have been discussing about efficacy. I wanted to actually ask a little bit more, explore this a little bit more.

We have heard a bit that the side effect profile, one component of it that we're concerned about, the episodes of orthostatic hypotension and syncope may be related in part to an alpha blockage effect. That implies that some component of the efficacy during exercise and perhaps reduction in use of nitroglycerin might also be related to this pharmacologic effect, at least at higher doses.

When one thinks about that in the larger setting of use of alpha blockers for cardiovascular indications, one thinks about the experience several years ago of use of alpha blockers in heart failure, in which efficacy based in part on their effect, but not all. Their effect on vasodilation dissipated and was lost over time, and we often called that, for lack of a better word, tachyphylaxis.

One of the things that troubled me a bit in hearing the discussion today and the sponsor's interpretation that side effects are attributable to alpha blockade, is the issue of whether the anti-anginal effect is, in fact, sustained, because your control study, CARISA, went out only for 12 weeks. Is

that correct?

DR. WOLFF: Correct.

MEMBER LORELL: So do you have a database with something more than, say, use of nitroglycerin, but something like exercise duration that shows that benefit is sustained for many months and not lost after use for a few weeks?

DR. WOLFF: The longest controlled experience is the three months of the CARISA Study.

MEMBER LORELL: How about a withdrawal study for a longer period of time showing a drop in exercise performance?

DR. WOLFF: We did the withdrawal study, but we did it right at the very end of CARISA, so that was three months experience, as well. We also have withdrawal data with the immediate-release formulation, but if memory serves me correctly, it was also either six weeks or 12 weeks, I can't recall, of continuous treatment and then withdrawal. And we did see what you would expect, which is in the patients that were withdrawn, there was a decrement in their exercise times back to a baseline level, but we don't

have a longer controlled efficacy experience beyond the three months of CARISA.

MEMBER LORELL: Could you speculate or comment for the Panel knowing this earlier experience of a little more than a decade ago about loss of efficacy with alpha blockers and heart failure as to what data you might bring to bear or comments about that?

DR. WOLFF: I think that data on the changes in rate-pressure product relative to the changes in exercise duration are probably the most instructive. I wouldn't disagree that at the very highest doses that we studied in concentrations, because there are slight decreases in the end exercise systolic blood pressure, that there may, in fact, be some contribution from an alpha blocking effect at those doses. It can't be excluded from these data.

The only thing that I can say is that alpha-1 blockade, while it could have some contributory aspect to the overall efficacy of the drug, as we discussed a bit earlier, it can't underlie it completely, because really in the absence, I think,

of any change at all in blood pressure, heart rate or rate-pressure product, we still are able to demonstrate statistically significant improvements in exercise duration. And again, whatever the mechanism of these small reductions in rate-pressure product, they happen in this trial to be greater at trough than at peak. They also were at 1000 milligrams twice a day in the MARISA Study, as well. And yet, the exercise effects are generally greater, as you would predict, at peak than at trough.

So, I would agree. There could well be some minor contribution, but it can't be the entire explanation for the efficacy of the drug, because we can demonstrate the efficacy in the absence of any clinical profile consistent with alpha blockade.

CHAIRMAN BORER: I think it's worth having a clarifying statement here and perhaps, Bob or Doug, you will want to comment before you ask your next question, please. There never has been a requirement for showing persistence of effect for more than 12 weeks for an anti-anginal drug, so unless there was an a priori expectation of lack of effect persistence,

one might not have expected the sponsor to have done such studies. The 12 week standard was set only when nitrates were found to lose their effect at six weeks and before that, I think it was six weeks that was required. So, it's not an unreasonable question, but we probably want to be reasonably certain that there was some strong suggestion of loss of persistence of effect before changing the standard, I think. Bob?

DR. TEMPLE: What we usually get, usually is hard to talk about. There are not a lot of angina drugs being developed lately, but what we usually get is an active control trial without a placebo, because who would want to be in a placebo for six months to a year, that shows nothing, obviously, bad. That is not at all satisfactory. What we would like people to do is do a randomized withdrawal study after this active controlled trial. So, what they did was great. Ideally though, it would have been done after six months or 12 months of open-label therapy. Then you would show persistent effect that way and that would be better. But it wouldn't be true to say we have required that.

DR. THROCKMORTON: We have sort of offered up in other areas, in blood pressure for instance, where you could make exactly the same criticism where very little long-term controlled data that allow you to say you know the blood pressure effect persists beyond the controlled trial expansion period, randomized withdrawals out of six months or something like that demonstrating persistence of antihypertensive effect. So it seems like an important enough thing that we would want to be thinking about labeling a product that actually had that kind of data and brought it to us.

DR. TEMPLE: And that has been done for so many hypertensive drugs, but not all, and we have not required it. It has also been done for antidepressants and things like that. It's very informative. It tells you about maintenance.

MEMBER LORELL: No, I thank you for that comment. I think the reason I asked that this afternoon was getting a little fuller feel of the contribution of alpha adrenergic receptor blockade to the entire profile of the drug.

CHAIRMAN BORER: Blase?

MEMBER CARABELLO: In that same line, I noticed that in combined MARISA and CARISA, there were about 400 or so patients between the ages of 65 and 75 if I have got that right.

DR. WOLFF: Ten percent of the study population were older than 75 and yes, so there is about a third.

MEMBER CARABELLO: And in --

DR. WOLFF: So it's on that order, yes.

MEMBER CARABELLO: And a number of them, about three quarters of the whole patient population, were men?

DR. WOLFF: That's correct.

MEMBER CARABELLO: Yet, I noticed there were no reports of urinary retention as a side effect. Is there any evidence that urinary retention actually went down with the agent, because, I mean, obviously that would be great to have an anti-anginal drug that also helped you to pee and also might speak to this alpha blockade issue.

DR. WOLFF: It wasn't a signal that came

up. Again, I think in the plasma concentrations that are going to be experienced by the great majority of patients receiving the drug if it's approved, there really isn't much in the way of alpha blockade and you really kind of have to get to end exercise to see anything that we might attribute to it, but no, there was no signal.

MEMBER NISSEN: It's particularly useful when you get to be as old as Blase.

CHAIRMAN BORER: Well, for someone who wasn't born yet in 1982, I guess you can say that. Steve, you had another question to raise?

MEMBER NISSEN: This is really not at all an approvability issue, but it's a curiosity issue. You know, we know that patients with angina have both painful ischemia and silent ischemia and I know some of your consultants are rather expert in this area. Did you guys do anything looking at Holter monitor or evidence of changes in evidence of ischemia other than the exercise testing? I'm just curious as to whether there is evidence of an effect there.

DR. WOLFF: We didn't do Holter monitoring

in the pivotal studies. We just don't have that data.

MEMBER NISSEN: Yes. It would be interesting to see sometime.

DR. PRITCHETT: But I thought you told us you did have some Holter data from the early immediate-release data looking at silent ischemia.

DR. WOLFF: I believe the Study 1513 actually did contain Holter data, but the doses in that study were 30, 60 and 120 milligrams.

DR. PRITCHETT: Oh.

DR. WOLFF: Three times a day and they weren't effective, so those data aren't helpful.

CHAIRMAN BORER: Okay. If there are no other questions that need to be clarified before we begin discussion, we'll move on to a structure discussion within the context of the questions we have been given. I want to reiterate to the sponsor that all of us believe that the presentation has been excellent. It is credible, forthcoming and I think you have answered our questions as best as you can with the best data that we can see.

The FDA has asked for some specific advice

and I will read through this rather than summarizing it. Since I don't believe there are any formal votes that are requested here, we'll discuss, but I will ask people around the table to contribute, so that we get a reasonably representative view of some on these issues and some perhaps can be dispensed more summarily.

"The Cardio-Renal Advisory Committee is asked to give an opinion on the next steps in the Ranexa Development Program. Ranexa (ranolazine) is under development for use as an anti-anginal agent. It is unclear which of its pharmacological properties contribute to clinical efficacy, but the Agency review concluded that it is an effective anti-anginal drug.

The letter of October 30, 2003 communicating an "approvable" action listed the following deficiencies that are the subject of discussion today:

Inadequate safety experience with the sustained-release formulation and doses in the range proposed for marketing; inadequate evidence of

effectiveness in a setting commensurate with the risk associated with effects of ranolazine on ventricular repolarization; inadequate information on dose-response and dosing interval.

The ICH E1 recommends that drugs intended for chronic use have a safety database that includes at least 1,500 individuals treated with relevant doses and 100 patients treated for at least one year. Greater exposure is recommended if there are specific concerns." And we have a table that summarizes the available data for ranolazine, which we have all heard and it's in the questions that most of you had.

This is a background. We have several specific questions. First, "Evaluate the following factors as influencing the need for additional safety data: 1.1. Availability of other approved anti-anginals." We're dealing here specifically with the issue of the need for safety data in light of the fact that there are other anti-anginals available. Does anybody want to discuss that? Ed?

DR. PRITCHETT: Well, I'll just comment and say that in general, I believe in pharmaceutical

innovation. We have heard that there aren't a lot of other drugs for angina being developed today. This is apparently some form of novel mechanism. Although, I don't think we know exactly what the mechanism is, but it's not a calcium channel blocker. It's not a beta blocker and it's not a nitrate. And so I think there is some merit in a new compound with a new mechanism for this indication.

So, I think the fact that it is novel in some ways is good. Although, the fact that it has this, you know, sort of modest QT effect and the fact that it comes from a new class and a class that we don't have a lot of other experience with, you know, is perhaps worrisome. So I think it cuts both ways, but in general, I applaud the development of new, innovative therapies in new classes.

CHAIRMAN BORER: Let me push you just a little bit. I don't think anybody here would challenge the idea that a new anti-anginal drug that is effective and acceptably safe for its intended use is a good thing to have. Gene Braunwald laid out the case and we all believe it.

I think the issue here is given the fact that angina is a symptom and that the drug is intended to prevent the development of a symptom, not to make people live longer, not to make heart attacks less common, but to relieve a symptom. Do we have sufficient information now about the safety of this drug, so that we can approve it, given the fact that there are some other ways to at least partially relieve symptoms, this might make things better, but there are other drugs available? Do we need more information about safety, because, in fact, the purpose of the drug is to make people feel better, rather than to affect additional natural history endpoints?

DR. PRITCHETT: I guess I'll stick my neck out here and say I think that there are some things that make us feel good here. This is a drug that has been in the hands of investigators, who are cardiologists, who have easy access to electrocardiography. It's not like a drug that is being worked up by psychiatrists or allergists or gastroenterologists who don't routinely do these

things.

I guess the case that I'm coming around to making, the fact that the people who worked this drug up and never documented a case of torsade, I think, is kind of encouraging, because I think these are people who could have done it if it occurred, because they have ECGs available to them and because a lot of ECGs were done during the course of this study.

Now, our colleagues from the FDA will tell us that the database presented on behalf of bepridil dwarfed this and it still turned out to have torsade. So I'm not saying that there won't be a case of torsade with this drug at some point in time. In fact, I think there will be one, because I have seen it in placebo-controlled studies, so if patients on placebo can have it, then patients on ranolazine can have it. But I think that the QT interval prolongation that we have here is pretty modest. You know, in my sort of calculations that I did, I sort of came up with about 8 milliseconds. You know, it's not five or less, but it's not 20 or above. And so I think we can -- I am reassured by the absence of a

documented case of torsade.

There are some things here that I don't understand. I don't understand the interaction of hepatic disease and the QT and, you know, the syncope is a little bit funny, but I am encouraged by the fact that we have electrocardiograms recorded during syncope and, you know, they haven't shown an arrhythmia. I think with respect to the mortality data, somebody asked is this reassuring or is it no information? It's virtually no information.

CHAIRMAN BORER: Bob?

DR. TEMPLE: I just want to be sure that we were clear. There are two sets of questions. One are questions related to specific concerns like syncope and QT and stuff like that. That's one set of concerns. The other was just the total exposure, which this is about -- for total exposure, this is about sort of half of what we would expect. It's not nothing, obviously, and we don't think there is any deficiency at all, according to usual standards, in how much exposure there was of more than six months a year. That is the usual exposure for better or worse.

It's the, you know, reasonable dose, acute exposure that's a little low. So we're just asking, you know, how do you feel about that?

DR. PRITCHETT: Well --

DR. TEMPLE: Because there is a principle that if you get more, you can lighten up on the demands.

DR. PRITCHETT: But I think --

DR. TEMPLE: Usually, one is thinking of, you know, survival and stuff, but not only.

DR. PRITCHETT: But I think, you know, I agree that the number of patients and the length of exposure is a little bit and compared with other things that you see. Part of the reason is is because they have been lucky and nothing very messy has shown up that has driven them to say well, we need, you know, another big study. You know, we need another big Phase 3 study. It's this anxiety, you know, the sort of background anxiety. So I agree it's not as big, but, you know, except for the 8 millisecond QT prolongation at the 1000 milligram dose, you know, not a whole lot has shown up that worries me.

DR. TEMPLE: I'm not disagreeing with that thought.

DR. PRITCHETT: Okay.

DR. TEMPLE: I'm just trying to make sure it's clear we were asking one thing about the specific things and the other as a sort of general matter, this is what you usually do. I should say that bepridil was -- there were cases of torsade right in the database. It was a piece of cake to discover that just as it is with sotalol. We don't think this is anything like that. And the drugs where QT has been a concern, we don't think the rate is going to be one in 100 or one in 500. It's the one in 5,000, the one in 10,000 that people are worrying about. So, we would never say that for a drug with this degree of impairment, you have to do enough cases to rule out that, you know, there is one in 10,000. That's not doable. There wouldn't be any drugs if you had to do that.

DR. PRITCHETT: Well, then we both agree in innovation.

CHAIRMAN BORER: Blase and then Steve?

MEMBER CARABELLO: I suspect with regard to electrophysiologic safety that the sponsor has, in fact, set a new bar at a higher level than we have seen. That is to say that the preclinical data, which are elegant compared to the sort of blunderbuss approach of the QT interval may give us more reassurance than we have ever had. Now, unfortunately, we won't know that until after there has been greater exposure to the agent, but I must say I was very persuaded by the preclinical data that this agent is electrophysiologically safe.

DR. PRITCHETT: I guess I just have to address that and say I am unmoved by the preclinical data. I think it's nice. I think it's elegant. We have had a beautiful exposition of it. I am just a country doctor from a rural state and I am interested in what happens when the drug is given to patients, and I am far more impressed by the clinical observations than I am by the elegant electrophysiology, which congratulations to all of you. It's superb work, beautifully presented. I enjoyed it.

CHAIRMAN BORER: Steve and then Susanna.

MEMBER NISSEN: Yes. You know, I sort of read these questions somewhat more literally, so I'm going to see if I can answer a little more literally. I do think that the availability of other approved anti-anginals does play into my thinking about this, and let me see if I can articulate it. If you have a drug for pulmonary hypertension, as we have considered at this Panel, where there is very little we can do for these patients. They are desperately ill and we have almost no oral drug. You know, we set the safety bar pretty low, you know, for a drug that, you know, bosentan, that had major safety concerns.

So, on the other hand, if you have three classes of agents that are available to treat angina and we have no study where those agents were used maximally that showed that this agent, in fact, could produce a benefit beyond what we could achieve with conventional therapy, then that does, in fact, play into my thinking about how much safety data we need.

So question 1.1., if I understand what you're asking, is does the availability of other

approved anti-anginal agents play a role on how low we're willing to drop the safety bar and the answer is yes, it does play a role. And I'm not saying this drug isn't safe, but in terms of looking at this as in the big picture, it does play a role. And I have different answers for the rest of those questions, as well.

CHAIRMAN BORER: Susanna?

DR. CUNNINGHAM: Well, when I think about who will probably be consuming this drug once it's available, I think it will probably be a fair number of females and some greater ethnic diversity than has been studied. So I think in terms of both efficacy and safety data, we need more data on women and we need more data on diverse populations as regards to ethnicity.

CHAIRMAN BORER: Okay. And that conclusion is driven in part by the fact that there are other drugs that you know you could use in the interim for those people.

DR. CUNNINGHAM: Even so, we don't know. There are only 23 percent women in CARISA and MARISA

and, if I remember correctly, it was only five percent ethnic minority and that's not representative of the population of the country.

DR. THROCKMORTON: Susanna, could I just ask you a little bit more about that? Yesterday we talked about how the Agency sort of thought about subgroups in populations and we have, of course, been tasked with looking at three of them, in particular, and we hadn't done -- we hadn't looked as carefully as we do now in the past, obviously. One way to handle that is through labeling, to say what's known, to say what's not known, to allow the informed physician and consumer to make a choice.

The alternative is to sort of say no, you know, this is an important enough subgroup to say we really do require information. One thing that might play into that would be if you had a signal, say, that you believe to be credible that one group was less -- there was less efficacy in one group or the other or you might just say no, you know, including it in labeling is sufficient, that, you know, what we have is available, say, at the labeling. And I'm just

curious where you view, I guess, females in particular, but heart failure and the other sorts of things we have been talking about.

DR. CUNNINGHAM: Well, in the FDA analysis, they have indicated it was much less effective, if not not effective in women. So I think we would like to know if it's effective in women. I think that would be a key piece. And since there is really no data on ethnic minorities, it's difficult to say if there is a signal or not of there being a problem, because we don't have enough to decide. So I guess you could put it in the labeling, but that's not serving the population well, because they are going to get it no matter, one way or the other.

CHAIRMAN BORER: Beverly?

MEMBER LORELL: To pick up on Dr. Cunningham's comments, I think that it might be easy to sort of sweep the issue of efficacy in women aside a little bit and just say well, yes, yes, this is seen in multiple classes of anti-anginals. I think the problem here, as Dr. Pritchett alluded to, is that whereas we saw absolutely elegant preclinical data

about the interpretation of the long QT, it is still in part hypothesis generating. And we do know from experiences with other drugs and torsade of an increased propensity of women.

So, I guess, I'm a little bit troubled by that interface that we're using, talking about adding a drug on to treat a symptom. We're talking about perhaps tolerating its labeling for a group for which there is minimal evidence of substantive efficacy in women, but also with a group that we have a heightened concern about safety issues, particularly if this drug were used very broadly or were used as it was in CARISA, as a number two layer-on drug to a low dose of a first one.

DR. THROCKMORTON: So, very similar to the sort of conversations we had yesterday, I guess, in terms of the gender interaction there, too.

DR. TEMPLE: I just wanted to make one comment about racial mix. We have been tracking this and there is no question that now that more data are coming from foreign sources, the fraction of black people in trials is dropping down, and we don't have

an immediate easy answer other than to say, you know, you better do your studies in the U.S. or someplace else where there is a proper mix. We have not said that so far, but we're watching it and are troubled by it.

The relatively small number of women in the trials is consistent with the past, and I believe it's because there are age limitations and women catch up a little later. And if you had a large fraction of elderly populations, you probably have a high fraction of women, but these don't for the most part. But I don't know that that's true. That's just my explanation. Twenty percent is a little lower than usual. The other factor is there is not a lot of controlled trials here. Sometimes you can pull large amounts of data from multiple trials and get an answer that you couldn't get from the individual trial. You don't really have that opportunity here.

CHAIRMAN BORER: Steve, go ahead.

MEMBER NISSEN: Well, you know, it's interesting. I want to disagree with Ed on something and agree with Blase. I'm actually not reassured by

the absence of torsade in the clinical exposure to date. To me, it doesn't influence me one way or the other, because if you actually make the calculation of what the 95 percent confidence limits would be around, you know, what rate could you have had and missed? It's so low, as to be essentially clinically meaningless.

So we simply don't know whether this drug will produce torsade in man on the basis of the exposure to date. So I just think that that's not helpful nor is it likely to be made more helpful by adding another 1,000 patients, because, in fact, we're not going to know that before this drug, you know, goes to market.

DR. TEMPLE: No, that won't help you. How do you feel about the choice of dose with respect to that? I mean, if you get down to relatively low doses, you're probably talking about four milliseconds, usually not considered a problem, except that this is a drug that has very variable blood levels.

MEMBER NISSEN: I want to --

DR. TEMPLE: What do you do with that?

MEMBER NISSEN: I want to pursue that just a little bit further and let me just say, Bob, that I was pretty impressed by the preclinical data, as well. You know, I thought that, you know, I recognize that it isn't definitive and that we're going to need several years of additional information and testing of a lot more drugs, but it sure made me feel a whole lot better about the degree of QT prolongation that we saw here. And, you know, now --

DR. TEMPLE: You were supposed to.

MEMBER NISSEN: Yes, now, of course, I was supposed to. Well, but, I mean, you know, the sponsor did a nice job there. I mean, you know, your audience was the Committee and you convinced a lot of us that you had something important to say from the preclinical data. Having said that, I'm not sure I want to bet my patient's life on the preclinical data, and that was a very harsh way of saying it, but it's reality.

And, so, what is going to have to happen here is that this drug, I think, will ultimately be

approved and I think we'll have to have vigilance and we'll have to look for these episodes. We're not going to see it before the drug is actually released, because there is no amount of safety data that you could reasonably ask, no amount of exposure data that you could reasonably ask the sponsor to produce that would sufficiently reassure me that an eight millisecond QT prolongation is of no consequence. But I do think the preclinical data went a long way to making me believe that there is a very good chance that when generally and widely exposed, that the drug is not going to hurt people, and that makes me a lot more comfortable.

DR. TEMPLE: But would you comment specifically though on what effect, if any, the limitation of dose to, say, 750 twice a day would have on your thinking, because the mean effect is much lower there than on 1000 or 1500?

MEMBER NISSEN: Well, I don't think that's such a big deal here, Bob, and I'll tell you the reason why. If there is a liability the drug brings to the table, it's the kind of drug-drug interaction

liability. If you think about the drugs that we have gotten in trouble with from QT prolongation, they are drugs that prolong the QT modestly, but then have a 3A4, an interaction with 3A4 inhibitors. I mean, that is the signature of a drug that gets people -- one of the signatures of drugs that gets people into trouble. And so --

DR. TEMPLE: Okay.

MEMBER NISSEN: Yes.

DR. TEMPLE: That's true.

MEMBER NISSEN: Yes.

DR. TEMPLE: But when you interfere with the metabolism of terfenadine, you multiply the blood level by something like 20.

MEMBER NISSEN: Yes, yes.

DR. TEMPLE: 20, not 3.

MEMBER NISSEN: No, no, I mean, listen, I'm not telling you that this is --

DR. TEMPLE: Amounts matter.

MEMBER NISSEN: Yes, this is not the ugliest 3A4 interaction I have ever seen, but when a drug that is commonly used to treat the disorder that

we're interested in, namely diltiazem, in a dose that is commonly used, produces a 2.4-fold elevation.

DR. TEMPLE: Right.

MEMBER NISSEN: And when I know that my colleagues don't read product labels that way, you know, they should and maybe even I don't. You know, I'm sorry to tell you that, Bob. I know it's shocking.

DR. TEMPLE: This is terrible.

MEMBER NISSEN: But, you know, it gives me cause for concern and that is why, you know, I actually -- there are some other questions in here, including the question about this high-dose intravenous infusion study, I actually think that was very helpful to me, because I could see what would happen if you went to the point of very serious toxicity. I mean, they pushed this drug about as hard as I would have been comfortable. I'm not sure as an investigator, I would have been comfortable doing that, but they did it and they didn't see anything really ugly on the QT side when they did that.

And so now, I ask the question if you give

a 3A4 inhibitor, you know, are you likely to get into that, to get concentration range that is so high that you're going to see terrible trouble? And the answer is probably not.

DR. TEMPLE: Well, they have pretty good data on the effect of 3A4 inhibitors. It's sort of two-ish for the weaker ones and up to four for the big guns.

MEMBER NISSEN: Yes.

DR. TEMPLE: I guess I just want to press this a little more, because I'm sure it's going to come up in any discussions. The further away you get from the doses that cause problems, the more you have a little buffer against the inadvertent exposure to a 3A4 inhibitor, the possibility of a little bit of liver injury and, you know, you move away. And, so, I'm still interested in hearing what everybody thinks about whether that's reassuring and if so, how much and what you think about that.

CHAIRMAN BORER: Tom?

MEMBER PICKERING: Yes, I would like to return to a point I made earlier with regard to the

other anti-anginals that if we're administering this medication, the only reason we're doing it is because we think the patient is going to feel better. And if you're a cardiologist, you're not going to do a treadmill test, put the patient on ranolazine and do another treadmill test and say look, you have got 23 seconds improvement, so you are better. You are going to ask the patient do you feel better?

And we really haven't heard any evidence one way or the other whether patients liked being on this, and I think the fact that it does prolong the exercise time, which I certainly accept, is not the same thing, because to take the example of beta blockers, they may make people be able to go longer on a treadmill, but they may become depressed and feel slowed up.

And we have heard that this medication also has side effects. So I don't think we have a sort of -- and you may say it's a soft endpoint and it is, but there are measures for measuring patient preference and quality of life, and I'm sort of disappointed that we haven't heard anything about

that, because I think it would make a helpful reference frame for when we're actually using it in real life practice.

CHAIRMAN BORER: Yes. We have sort of a poor man's index, which would be reduction in angina attacks per week and reduction in nitroglycerin use, but there is no quality of life information, I guess. Ed, you had another comment?

DR. PRITCHETT: Yes. I just want to comment on the question of what the torsade incidents could be. I mean, we have zero incidents, zero cases of torsade in a database, you know, all comers, 2,700 patients. You know, there is a statistical rule of thumb that tells you that the 99 percent upper confidence limit of the point estimate is 2,700 divided by three, one out of 900. So, you know --

DR. TEMPLE: Ninety-five.

DR. PRITCHETT: Yes, 95 percent, so it's, you know, it's one out of 1,000 around is what our point estimate could be. That is a whole lot lower than what we see with a lot of anti-arrhythmic drugs and things that electrophysiologists are used to

using. Now, I understand all the caveats. I mean, a lot of these patients --

DR. THROCKMORTON: Duration counts.

DR. PRITCHETT: That's right. Duration counts and that sort of thing, but, I mean, this is in what my college physics professor used to call desperate physics. You have taken the numbers you have and trying to do something with them. But in any event, you know, if you had to use it, if you had to take the numbers we had and use them, fine. You can pare it down. Say they only have, you know, 1,800 relevant patients, you know, then it's one out of 600. You know, but you can come up with a number that tells you that the point estimate for the rate of torsade per patient exposed is way less than what a lot of other drugs are that are out there that cardiologists are using.

MEMBER NISSEN: So if the rate were really one in 600, you would not consider that an approvability issue? In other words, I guess, my issue would be is if the rate were really one in 600, would you approve this drug as an anti-anginal? And

the answer is I probably wouldn't.

DR. PRITCHETT: I probably would.

MEMBER NISSEN: Okay. That's interesting, because, you know, what was the rate? Let me ask you a question. What was the rate of torsade with terfenadine, another drug for symptomatic relief?

DR. TEMPLE: Zero. You don't get any until you interfere with this metabolism.

MEMBER NISSEN: Yes.

DR. TEMPLE: And it also wasn't discovered for three years, too.

MEMBER NISSEN: Yes. You know, to me, Ed, I guess I'm trying to make the case here that I just don't think we know.

DR. PRITCHETT: Right.

MEMBER NISSEN: You know, I am reassured by the preclinical data, but the true incidence here will not be known for several years, and it could be high enough that it could ultimately lead to the withdrawal of the agent within the range of rates that are possible given our current clinical database.

DR. PRITCHETT: I think that's always

true, that something will show up after a drug is marketed that will wind up it being withdrawn. For my money, when I'm trying to figure that out, I will put my nickel on what was seen in the clinical program, though, not the preclinical program.

DR. TEMPLE: The drugs that have caused torsade while you have the needle in, things like sotalol, bepridil, dofetilide, there is nothing to it. It's one percent. It depends on the dose. But other major drugs that are a problem, cisapride didn't turn up any, astemizole didn't turn up any, and that could be because you needed to interact with them or give too much or something like that. But, you know, they caused plenty. Nobody thinks this is like bepridil or something like that.

CHAIRMAN BORER: Okay. I want to move on from 1.1. here where we are. I think we have had some wide ranging answers and maybe we can telescope down just a bit as we move on, but we began to discuss, and Beverly actually responded to the nature of the efficacy demonstrated to date as a basis for perhaps impacting on her need for more safety data to provide

an adequate description of this drug for consideration for approval.

Paul, do you want to discuss that issue, as well, the nature of the efficacy demonstrated data and its impact on the need for additional safety data?

MEMBER ARMSTRONG: Well, for me the efficacy does begin to level at 750, but I think there is some evidence that 1000 gets you more, and my principal -- and I am moderately convinced that there is durability of the effect, but would like to see longer exposure both from the standpoint of safety and efficacy. So at this point, I am moderately confident that the dose range that has been suggested is reasonable and it would be safer at 750 than it would be at 1000, but not much, and there would be some more efficacy at 1000 that there isn't at 750. So I'm pretty flexible.

CHAIRMAN BORER: Okay. If there were more efficacy data, that is, if the dose-response relationship had been worked out a little better than it has been, if we had two pivotal trials that were clearly demonstrative of efficacy rather than one that

is clearly demonstrative with no clear dose-response relation and another about which one might raise questions, and perhaps we will raise the questions later or maybe we won't, if you had more compelling information about efficacy, about dose-response, about sub-populations, about drug-drug interaction, well, that's a safety issue, but about the additivity of this drug on top of other drugs, if we had more of that, would that lower the bar for requiring more safety information or would it have no impact?

DR. TEMPLE: You would have the safety data.

CHAIRMAN BORER: Well, maybe we do.

DR. TEMPLE: I mean, I guess I've got to be clear. You're saying if there were additional studies that did this, because then they would have 400, 500 people and it wouldn't look so different anymore.

CHAIRMAN BORER: Right. If the data were available in the current data set.

DR. TEMPLE: Okay.

CHAIRMAN BORER: Okay. Well, we'll come

back to that.

MEMBER NISSEN: Let me actually answer it if I could. You know, I do think that if we had more data, I mean, I do think if we had more very elegant, more elegant dose-response data from CARISA, it would be helpful, because, you know, Bob is raising this question. He raises a very good question. You know, why not limit it to 750, because we don't see any more from 1000? And so the uncertainties about dose do have an effect on how we interpret safety, because if, in fact, we really did know that 750 was the top dose that we needed, then it would mitigate a little bit against some of the safety concerns. We would know we didn't have to push the dose in order to get efficacy. So, I think that safety and efficacy here are interwoven. They are interrelated and the more rigorous and the more useful the efficacy data, the more one can be comfortable that we know enough to be able to move forward.

CHAIRMAN BORER: Ed?

DR. PRITCHETT: Well, I mean, I think choosing a dose-response, choosing your doses from

this data set is really sort of a charming exercise, because we have the MARISA Study with 500, 1000 and 1500 in it, you know, which has three doses over a threefold dose range, but there is a study design that has some problems with it. Then we have this very nice parallel design study that has the 750 and 1000 bid in it, and they are indistinguishable on all their outcomes.

So if you believe that 750 and 1000 are indistinguishable, then how do you account for the fact that 1000 and 1500 show an efficacy difference in MARISA? So, I believe there is a continuum of these doses and, you know, frankly, I am intrigued with the idea of the 500, you know, 750 or 375, 750 as doses, but I am also not terribly troubled by 1000, you know, as the upper limit.

CHAIRMAN BORER: Ed, do you believe that the MARISA trial does show a difference between 1000 and 1500? The statistics don't say that. What they say is that there is a difference between each of the three doses and placebo.

DR. PRITCHETT: Yes.

CHAIRMAN BORER: And I would guess, although we didn't see the data, I would guess that if one did an analysis and accepted -- forget about the study design and the possibility for carry over and what have you, and the training effect or the learning effect or whatever it is. Forget about all those things. If you look at those numbers, it would appear that there is a dose-response curve, that there is a dose-response relationship.

DR. PRITCHETT: Yes.

CHAIRMAN BORER: That it's different than zero. The slope of that line is different than zero. But remember that 1500 isn't going to be used, so we have two doses and do you believe that the data are sufficiently robust, not to use that word, so that you can say there really is a dose-response relationship within the range of the doses that would be used?

DR. PRITCHETT: Well, I think that the exercise of pulling your doses out of a data set like this requires both statistics and common sense, and I don't think it requires that we have a study that shows that the doses that we want to use are

statistically different from each other. You know, I think, you know, we can say that they numerically show something, but I don't think there is either a regulatory or a common sense requirement that the studies have to be powered to demonstrate a difference between two adjacent doses.

MEMBER NISSEN: Even when there are safety issues.

DR. PRITCHETT: Yes. Like I said, I think picking doses, you know, when you have got -- you know, we have got five doses that have been tested from two different studies using two different study designs, and you can throw up your hands and say I don't know what to do with that or you can say that's interesting, that's an interesting problem, let's see what we can do.

CHAIRMAN BORER: I don't think there are five different doses from the two studies. I think there are three different doses and placebo.

DR. PRITCHETT: They tested 500, 750, 1000 and 1500.

CHAIRMAN BORER: Four, four, I'm sorry.

DR. PRITCHETT: Four doses, one of which we have all decided we want to discard, the 1500.

MEMBER NISSEN: And can I ask you about this? Let's suppose this drug didn't produce syncope, didn't produce dizziness and it didn't prolong QT, didn't do any of those things, would we be having this discussion about whether it should be 750 or 1000 or, in fact, does it implicitly have something to do with our comfort level about safety? That was what you asked, Bob.

DR. PRITCHETT: Yes. No, and I think it does.

MEMBER NISSEN: And my answer is it does.

DR. PRITCHETT: I think it does have a little bit to do with that. I mean, I think we have tossed out the 1500, because the side effects are patient complaints, you know, but now we're trying to wrestle with the three remaining dose choices, the 500, 750 and 1000. And, you know, I don't have strong feelings, but I'm not -- you know, I'm not standing up at the ramparts ready to discard 1000 either.

MEMBER ARMSTRONG: Jeff, if I can just

defend the 750, 1000. To the best of my knowledge, the patient comfort in angina on a weekly basis bears little relationship to exercise performance on a treadmill. So I was actually impressed, coming back to what Tom was raising earlier, the issue of nitroglycerin consumption and angina frequency, which I think does show a dose-response in the CARISA you have cited, so that was the basis for my flexibility across, not the fact that the exercise treadmill times were flat. I think that's important. There is the same -- there is clearly no dose-response in exercise, but their data appeared to me to be a clinical dose-response that I think may be meaningful.

CHAIRMAN BORER: Yes, it may be, it may be, and I guess we'll have to make a judgment about that. Often one gets less places, less confidence in the nitroglycerin consumption data and the ambient angina data, because we really don't know how much exertion was involved in generating the symptom that caused the use of the nitroglycerin. Whereas, we do on a treadmill, but that's a separate issue and we don't have to get into it now. Beverly?

MEMBER LORELL: Well, I think there is an additional dose issue worth exploring and it's related to the safety issue, and it would be a non-issue if there weren't the angst about QT prolongation. I think that it is likely that, at this point in the drug's history, we're not thinking about it being used as initial monotherapy. So it's of great interest to understand efficacy by whatever measure on the background of something.

So to me, one of the points that was very interesting about CARISA is we don't have data, I don't believe, about the lower dose that is proposed as a second add-on drug to any of the background therapies that were used, so we really don't know whether it's efficacious in that setting. Is that correct?

DR. THROCKMORTON: That is correct.

MEMBER LORELL: Yes.

DR. TEMPLE: Right, but none of them really added on to good sized doses.

MEMBER LORELL: But we don't have data even on dinky doses.

DR. TEMPLE: At all.

MEMBER LORELL: Yes.

DR. TEMPLE: Yes.

DR. THROCKMORTON: Jeffrey, I wonder if we could go back to the 1500. The sponsors proposed that it would be a dose that would not be used, and I am wondering. It sounds as though at least, Ed, you're convinced by that and maybe you could help me understand what it is that convinces you of that. If you look at the adverse events, about a third of the people reported them in the 1500 milligram twice a day dose. Now, there is IV data I understand that informs us maybe, but if only a third of people had adverse events at least in a week, it seems possible that that would be a dose that whether or not it were approved, we can sort of anticipate dose creep.

Dose creep at least is a concept that has occurred in other settings, obviously. That is only relevant, because if we were thinking of using choices of doses to limit safety, we're going to only approve these couple doses, because they give us some sort of safety margin, that might work less well unless there

is another reason for people not to go higher. And so I just -- I wonder.

DR. PRITCHETT: Yes. I think that's a legitimate question. I would like to congratulate the sponsor for exploring a dose that turned out to be not one that they liked, you know, having the courage to go up in steps big enough to demonstrate that you got to the top of the range, including both the 1500 milligram dose and the IV, what did you call it, super tolerance study or whatever it was, but I think in the 1500 the thing that I was more impressed with was the sort of non-linearity of the number of side effects that were reported of the ones that we really thought really were related to the drug, nausea and things like that. And that is not to say that that's unacceptable, but it looked like a break point in the curve, so I'm willing to say that 1000 -- you know, I'm willing to say that the 1500 is probably not a dose that we want labeled, but it's also not a dose that I am alarmed if they wind up, if a patient winds up creeping up there.

CHAIRMAN BORER: Let's move on for a

moment here to 1.3. "Available safety data from short-term studies of the IV formulation." I think everybody who has spoken has agreed that these data decreased our safety concerns, so that's a good thing. 1.4. "Available safety data from the short-term studies using the immediate-release formulation." How much weight do you give to the safety data from the short-term studies using immediate-release formulation? Steve, would you like to?

MEMBER NISSEN: Sure. I mean, a little bit, but not a huge amount. For one thing, it's not the dose formulation that's going to be given to patients. What it does help me with though is that because the peak-to-trough effects are greater, then it does give me a little bit more of an idea what happens. If there are AEs that are occurring during peak exposure, then that's going to get unmasked with an immediate-release formulation, but I don't think -- I mean, unfortunately, it really is an unfortunate development program that it started out as an immediate-release formulation and then moved to a sustained-release, because it would have been so much

more useful for us to have used that exposure to understand better what was going on with efficacy and safety in the formulation that would ultimately be the one that would be chosen. So I suspect this occurred for other reasons, but nonetheless I don't think it's terribly helpful to me.

CHAIRMAN BORER: The sponsor made a good deal of and gave us a fair amount of information about the comparable blood levels achieved with the short-term immediate-release preparation and the sustained-release preparation, and tried to provide some comfort about safety, as well as efficacy from those data. Is that compelling for you at all? Does that help? Steve, why don't you continue?

MEMBER NISSEN: It helps a little bit. I mean, I think having the immediate-release data here is useful, but not as useful as having exposed the same number of patients to the sustained-release formulation. I mean, that is one of the problems here, is that our knowledge base based upon the sustained-release formulation is somewhat limited. And it's limited in part, because the total exposure

involves two different formulations of the drug, and I don't know the extent to which that was an issue for the Agency, but it is an issue for me in that I would like to see exposure at some greater level to the drug as formulated in the way that it's going to be administered to patients.

CHAIRMAN BORER: Okay. Does anybody disagree with that? If not, let's move on. 1.5. "The overall safety profile from the available data with the sustained-release formulation." I think we have discussed that already unless you want some additional comments. Doug? 1.6. "Available data pertaining to cardiac repolarization: Preclinical data." I think we have beaten that one down, too, unless you have a specific additional question. Okay. "Relationship between plasma concentration and QT interval prolongation. For example, the steepness, plateau of the effect," etcetera. Does anyone have any specific thoughts that are different from what we have said? Steve?

MEMBER NISSEN: Well, the only comment I would make is the steepness in hepatic patients is

just, you know, it seems like an extraordinarily unusual finding and one that, obviously, if you think about it, if it's 7 milliseconds for every 1000, well, if you say the dose range can be up to 5000, you can get 30, 35 milliseconds in a hepatic patient of QT prolongation pretty quickly. And so it's just one of those things that comes up that we need to know maybe a little bit more about.

CHAIRMAN BORER: We probably do. I would remind everyone that there were 16 patients, was it, that provided that data set? We didn't see the raw data, but correct me if I'm wrong, my guess is they were all over the map. That is that there was a fair variability. Is that correct?

UNIDENTIFIED SPEAKER: Do you want to see it?

CHAIRMAN BORER: Perhaps if you can just put it up. We don't need a long discussion. Just put up the slide.

MEMBER CARABELLO: But while that's coming up, it was also pointed out that none of us knew that 50 percent of patients with hepatic failure had QT

prolongations on no drug. I certainly wasn't aware of that. I mean, I think that's maybe an area where we didn't have a whole lot of expertise.

CHAIRMAN BORER: A very good point, but I think Steve's point is that there is a large unknown here and that the fact that the relationship between the plasma concentration and QT interval prolongation may be importantly different in people who have disease of the organ that is metabolizing the drug might cause us to want a little bit more in the way of safety data.

DR. JERLING: Yes. Here we have the data points separated by mild to moderate impairment. And I should say it's not only one or two. Half of the patients in each of the two cohorts had a response that was more than expected. Half did not. But in the totality of the data, we still see with some confidence that this is entirely different. It's not only noise. It's something else going on.

MEMBER HIRSCH: So the comment again is I have been calling for evidence of this change in QTc with structural heart disease, heart failure and

ischemic cardiomyopathy. This is certainly a patient group that will be receiving the drug.

MEMBER ARMSTRONG: Over half the patients had prior infarction in these studies, so there are certainly structural abnormalities. We have not seen the data, but we presume that a number of these patients would have left ventricular scars.

CHAIRMAN BORER: Doug?

DR. THROCKMORTON: Yes. This issue about, you know, sort of populational definition of QT is a little harder than usual here, because there is this indication that there is at least this one population where there is an uncommon response as far as slope of the concentration effect. Typically, the advice has been that if a drug is found to have an effect on repolarization, you do want to characterize it in the sort of relevant disease populations. You want to make sure that you don't miss a drug-disease interaction that we just don't have enough information from the available data to sort of predict.

So the questions I'm hearing from your perspective, that has not been adequately explored.

The sponsor has, you know, made an effort to explore those things and so I'm just trying to make sure, from your perspective, some relevant disease populations have not been looked at as much as you might have liked. Is that what I'm hearing?

CHAIRMAN BORER: Is that the general consensus? Alan suggests that there needs to be more data in patients with ischemic cardiomyopathy and other cardiac problems. Does everyone feel, believe that that's true or are we reasonably satisfied that we have seen a reasonable range of disease here?

UNIDENTIFIED SPEAKER: Women.

CHAIRMAN BORER: Yes. Women, we don't consider women a disease.

MEMBER NISSEN: Oh, don't bet on it.

UNIDENTIFIED SPEAKER: Absolutely.

MEMBER NISSEN: You may not.

DR. KNAPKA: You know, as a heart patient, I think no matter what disease you have data on, there is always something else. I mean, this could go on and on and on. I think sometimes you have to, you know, look at the data and be reasonably sure that

well, yes, there may be some other disease, people with other diseases and they can't tolerate this drug, but we're going to have to find that out and deal with that at that time.

CHAIRMAN BORER: I must say although, there are a lot of data I would like to have, a wider range of cardiac disease wouldn't jump out at me personally as one of the key deficiencies of this data set. I think there are other sub-populations we might want to know about, but as I looked, patients with heart failure of diverse ideology have been studied. They look pretty good. There is nothing to suggest that people with one disease or another form of disease do particularly poorly or have particular safety issues. Beverly?

MEMBER LORELL: I guess one question for the group, and I'm not sure how I feel about this, is that it was passed on very quickly today that the heart failure population was skewed toward a very healthy population in that Class III was excluded from this controlled data set that we have. So that's a healthy chunk of heart failure in a "real-world"

population, Steve's practice that we're talking about. So I guess that is a little nagging concern for me. I'm not sure it's a showstopper, but it's one thing to exclude end-stage Class IV, but to exclude Class III is a concern.

CHAIRMAN BORER: Okay. I mean, there are several ways that could be dealt with if we had no other problems and, you know, we could make that clear in labeling, put a black box on it or something.

DR. THROCKMORTON: Andy, is that true? Is that accurate that, in fact, we don't have any heart failure data, except in Class I, II or early?

DR. WOLFF: The MARISA and CARISA trials excluded patients with Class III and Class IV just because, basically, we wanted patients that were limited by their angina and coronary disease, and as they get sicker with heart failure, they wind up being limited by other things. But there are about 80 patients with Class III and Class IV congestive heart failure that we studied in a pharmacokinetic and drug interaction study, and the kinetics of the drug in congestive heart failure aren't remarkably different

from those, and this was now the more severe patients. So there wouldn't need to be dosing recommendations just based on plasma levels.

Then the second thing is the relationship between the QTc and the plasma level, and the slope of that relationship for patients with heart failure is actually slightly lower than it was for the general population. And similarly, with regard to structural heart disease, I mean, that point goes to that. And then when we looked at the population analysis of the Qtc, the patients with coronary artery disease also, which was most of the patients, had a slope that was no different from the healthy volunteers. So it would seem that that may go to Dr. Hirsch's issue.

MEMBER HIRSCH: That helps me. I hadn't quite heard that in detail before.

MEMBER NISSEN: Yes. There is one other thing. I mean, I know you made the case that it didn't make a difference, but it sure was disproportionate in how few patients had undergone prior revascularization. I mean, I do think it's nice when the patient population looks like the patient

population that we're most likely to give the drug to in the United States, and the fact is that everybody in the United States, most of our patients that have angina, have undergone some revascularization procedure and only a minority of those patients were actually included in studies.

And so while I don't think it's probably an issue, it always bothers me when the population for which a drug is studied for approval looks significantly different from the population that we're likely to administer the drug to, and this was a difference that caught my eye right away.

CHAIRMAN BORER: Yes. I would like to give a slightly different response on that particular issue, because we have raised it several times. I would say that there are several regions on the Island of Manhattan where the application of angioplasty may -- I'm not sure it's exactly as rapid, but it may approach the rate of application of angioplasty in the middle of Cleveland, but there are other places, in Brooklyn and in Queens and dare I say at the Bronx where that kind of response to angina isn't quite the

same, and my guess is that there is diversity all around the country.

And unless there were a biologic plausibility to suggest there should be a difference in response and the data suggested a difference in response, I just can't get too excited about that. The data don't suggest a difference in response. We saw the breakdown. It was the same in people who had prior angioplasty and those who didn't, which is consistent with my prior bias that there shouldn't be much of a difference. So although it would be nice to see more people, it would be nice to see a lot more people in every area, that one particular issue isn't a big thing for me. So you have now the entire range of responses having been --

DR. KNAPKA: Yes, but isn't this, I guess, the measure of any good research that your sample should represent the population that you're, you know, applying the drug or any other experimental results to. I mean, sampling is the key to everything. If you don't have the right sample, I mean, how can you apply it to anything? And I think that comes down to

women's issue, the race issue and everything else, that if you don't have the correct sample, the data becomes a little suspect I think.

CHAIRMAN BORER: Yes, that's certainly true and I think we're hitting that issue. I think it's just with regard to this one particular issue. It's not clear to me that the proportion of patients who have angioplasty and the proportion that doesn't has to mirror precisely the proportions in the United States, whatever those proportions are, which I don't know, except in Cleveland where I do know.

Okay. We have discussed the lack of torsade. We have discussed a number of other cardiac adverse effects. Well, maybe we haven't. Does anybody have any comments on other cardiac adverse effects reported in the database that have an impact on the adequacy of the safety database? Focus specifically on that. Beverly?

MEMBER LORELL: Yes. One of the issues that was raised last spring when QT prolongation was discussed here was the issue of whether there is additional or separate information contained in the

outliers. So in other words, the notion that I came away with from that very confusing session was that there might be mean and median data, but that there was something to be learned from people who were outliers.

So in hearing about this database today, I think we heard that about 2.3 percent of patients would probably be reasonably classified as outliers, and I guess one of the things that would have helped me a lot with this efficacy safety issue, knowing that we can't have an enormous study and wouldn't want to commission such a study to look for torsade in 20,000 people, was whether we have a strong enough handle on the frequency of outliers of that magnitude based on this relationship with disease and background therapy.

CHAIRMAN BORER: That's a good question and maybe we'll ask for a very short clarification from the sponsor, but my recollection is that the outliers were almost entirely people whose QTc increased by greater than or equal to 60 milliseconds, that there were very few people who actually exceeded 500 milliseconds. And, you know, the implications of

those things are not quite clear, but that's different from, for example, some of the other outlier sets we have seen here. If we can just have a short clarification, please, Andy.

DR. WOLFF: Okay. If we can just have the slide back from the core presentation since that's what patients have seen before. There we go. There was a clearer, and I think this is what was just said, effect of the drug to increase the QTc from baseline by more than 60 milliseconds than there was to have absolute values greater than 500 milliseconds.

The thing I would like to emphasize is that it's really not 2.3 percent of patients that I think we should refer to as outlier patients. They are patients who ever had an outlier value over an average of 14 or 15 ECGs obtained during the course of the study. The majority of those patients had a single outlier value or sometimes two. No patient has ever had the majority of their electrocardiograms show outlier values. So they are very sporadic, and I think they just represent the random variability in the data superimposed upon the linear increase that we

do see of 2.4 milliseconds per 1000 nanograms per mL.

There is a large component of regression to the mean that we can see. So in other words, the high absolute outlier values tend to occur more commonly in patients who begin in the upper half of the patient population. The large changes from baseline tend to be somewhat more common in the patients who start out in the lower half of the patient population.

But overall, I think what we have seen when we looked at the 3111 data and at the population analysis is that there is tremendous variability in this measurement, excuse me, both within patients throughout the course of the day and between patients. So if you have a slope of 2.4 milliseconds per 1000 nanograms per mL -- could we show the slope with the 95 percent confidence prediction? Yes. Great. Thank you. I mean, this is our slope and if you pick as a particular value for outliers 500 milliseconds, well, then as you climb up this slope and as you continue to oscillate fairly widely however around it, as you get higher up you're going to bump up against this more of

the time. But we would say that, you know, 2.5 percent of our values at any plasma concentration is likely to be up here and 2.5 percent are likely to be down here, and our database is exactly consistent with that.

DR. THROCKMORTON: Sorry, Andy. I have to say I wish I knew enough to agree with much of what you just said. The databases that we have, roughly speaking, are like yours where episodic QT prolongation above 500 milliseconds is viewed as a signal of alarm.

Now, I'm not saying I know that's, you know, an airtight thing. I would welcome any one of the 17 QT experts that you have available today, that that is what the data sets we have are, are intermittent ECGs that are collected and have QTs over 500. It's true that there is rationale for that perhaps, but that is what has been associated with a potential signal for risk by, in particular. The European community is particularly interested in that say.

The numbers, I mean, the other question is

whether the incidence that you have reported is different, and that is a little harder to get a handle on. I mean, very large data sets that Peter and you saw recently had smaller absolute incidence of QTs over 500 milliseconds in shorter term exposures I would say, and so whether or not that is exactly a comparable thing is hard to say, but it's probably not completely dismissable by reference to the known vagaries of collecting ECGs and measuring them and the intermittent, you know, sort of changes of QT.

DR. WOLFF: I think those other populations were actually not patients with cardiac disease also, is that not true, and their QT values were lower at baseline, I think, overall than where our patients began with coronary heart disease.

DR. THROCKMORTON: In that you trended towards 60 millisecond change from baseline and over 500 showing roughly the same story. I'm not sure where that takes you, but there may be some differences there.

DR. WOLFF: Yes.

CHAIRMAN BORER: Okay. Maybe we can cut

this particular discussion short. I think, Beverly, you have seen what is available and we'll have to come to a conclusion. Tom?

MEMBER PICKERING: Yes. I just wanted to make an additional comment about the syncope. I think I'm not really concerned about the syncope in the young people. You know, these are vasovagal episodes and they get up and they are fine, but in the older patients I think it is a potential concern and I don't care for many of these patients in this situation myself, but I think the prognosis in older patients for syncope is very different. You know, they can -- some of them may have orthostatic hypotension to begin with. They may break bones. They may hit their head. They may develop all sorts of other complications.

We have also heard there may be a very wide inter individual variation in plasma levels. I'm still not clear what the mechanism is. Is it an alpha blocker or isn't it? I don't know. So I think there is a sort of concern here that I feel hasn't really been resolved. I'm interested to hear what other people in the Panel think about the frequency of

syncope in a population like this.

CHAIRMAN BORER: So you're suggesting that perhaps there should be more safety data to help better define the frequency of syncope? Okay. Let's put a bookmark on that one. Let's move on to Question 2.

DR. THROCKMORTON: Sorry, Jeff. You left out, at least I didn't hear a lot of interaction from 1.6.3., which is really a fairly important one for the Agency.

CHAIRMAN BORER: Okay.

DR. THROCKMORTON: We really need to have some comment from you.

CHAIRMAN BORER: Okay. I'm sorry. I thought we had hit the hepatic impairment in some of the drug interactions, but if you would like some more.

DR. THROCKMORTON: Yes. Well, again, just to sort of focus it again. The issue here is, typically, we have not asked for interaction studies with individuals that have multiple risk factors for well, any sort of safety concern, but let's talk about

QT today. Typically, we have asked well, you know, how bad can you get if you have a maximum inhibition of your 3A4 if you have a 3A4 interaction? How bad can it get if you have another liability? But we haven't asked people to pile them on and so the question, the direct question is here we have a place where, in fact, we have got a very uncommon finding, this hepatic impairment. It's a thing that we haven't seen before.

How does that factor into the decision as to whether or not you need additional, you would recommend that we seek additional safety information about the consequence of more than one liability at the same time, so more than one drug or hepatic impairment plus CYP3A4 inhibition? Is that a thing that you see as necessary to be able to understand the effect of QT seen here or not?

CHAIRMAN BORER: Paul?

MEMBER ARMSTRONG: Well, I tried to winnow at this earlier, but I do think that this deserves a flag and I guess I would say that probably 90 percent of the patients that would be eligible for this drug

would be on a statin, and the frequency with which hepatic enzymes will be acceptably elevated in those patient populations or just at the upper limit of normal is probably quite substantial. So I did feel that that was an important issue. I raised the specter of the patient with a little heart failure and on a statin, which is also a common category of patients. I was somewhat reassured by the heart failure data that has been shown subsequently on that point, but I do think that that's a very common, going to be, drug-drug situation here that is likely to be relevant in a broad category of patients.

CHAIRMAN BORER: Okay. Are there any other combinations that we think specifically need to be studied to provide reasonable labeling? Steve?

MEMBER NISSEN: You know, I don't think I would raise the bar too high here, Doug. I mean, I guess the problem is you can drive yourself absolutely crazy trying to satisfy every potential drug-drug interaction and the reality here is that the risk that we're interested in, which is torsade, you're just not going to know until you get some post marketing

exposure. And so, you know, rather than wring your hands and make them do every imaginable interaction, I guess I just don't see it.

The only thing, the one that I would be interested in, and I suspect this is completely unprecedented, but here is a drug that is going to be used in a cardiovascular population, a lot of whom are going to get anti-arrhythmic drugs, and there has been the suggestion that this would not adversely interact with such drugs. Boy, I would sure like to know that. I mean, as a clinician who treats these patients, I would sure like to know that I actually had an agent like this I could give and not have to worry about whether they are also on a concomitant anti-arrhythmic drug, but I don't think I would ask that for approval.

I just think it would be very useful information to have, and I don't think I would not recommend driving yourself nuts trying to figure out every imaginable interaction, because the real question is is it going to cause torsade or not, and I don't think you're going to answer that question, you know, in the premarketing database.

DR. THROCKMORTON: Yes, it is a question of what you learn, but, you know, just as an argument you put two things together and all of a sudden the QT prolongs 60 milliseconds mean, and 25 percent of the people were over 500 on three successive ECGs. I mean, would that be useful information to you? And I'm not even saying I think that's likely. But again, with this relatively uncommon disease interactions, hepatic impairment, does that change the calculus is the question?

I'm not interested in driving anyone crazy and I try not to do things that are unjustified, so I will try not to do either of those things. But is this a case that's unusual? It's different than other drugs that I am familiar with. Does that change the safety equation, I guess, is another way of asking it?

MEMBER HIRSCH: I'll take the bait, because I keep sort of coming in here at the late moment. I mean, it does to a certain extent and I think that there is no answer to this. I always hate when the Panel or the FDA comes back and says now, we have changed the rules. You have a very

representative population. It's very reasonable. I would have designed a trial just like this, but aha, we have a new molecular entity. We have a little bit of discomfort despite the preclinical data and, in fact, the drug-drug interaction here is not random. One of them was diltiazem with a two to fourfold increase will be expected to occur frequently. Some doctors might even use it with verapamil and there will be additional structural disease and aha, there is that liver.

So there is -- I feel and share some of the concern. I just don't know if we can raise the bar at this time. We're likely to see, I think, adverse events and no way of testing it other than to see the post marketing torsade, unfortunately. I think the drug is less likely to be as well-tolerated as we have seen in these trials, but that will be a prescription in the physician-patient interaction problem.

CHAIRMAN BORER: Yes. In considering these responses, you know, the focus has been on torsade and that is very reasonable, but Tom pointed

out that syncope may, in fact, be a greater concern in this population and if, in fact, interactions of whatever sort lead to blood levels sufficiently high to promote the vasomotor instability that seems to occur as preparatory to syncope, then that might be a concern. So it's something worth keeping in mind.

Number 2, "Evaluate the following as factors influencing the need for additional efficacy data: Available data on effects of ranolazine on rate-pressure product or maximum oxygen utilization."

Let me try and respond to that and just disagree with me if you disagree, so we can move on to the rest. I think the issue of maximum oxygen utilization, rate-pressure product, etcetera, is all very interesting in that it deals with some inferences we could make about putative mechanism of action or pharmacological effects of the drug, I should say, and that would be interesting to know. I would say it's important only if we believe the safety data are not adequate relative to the benefit that we have seen, so that we have to be reassured that there is something new here. And I have got to tell you, that gets a

relatively low bounce with me. I would rather see the body counts. So I don't think that that really impacts in a major way, my thinking about how much efficacy data is needed. Blase?

MEMBER CARABELLO: I agree from the standpoint of efficacy that you don't need those data. I think you only need those data to make a claim. Well, I don't think we can make any claim about mechanism here. The agent works. Presumably, it relieves angina without lowering blood pressure very much or heart rate very much. Past that, I don't think we have a mechanism of action.

CHAIRMAN BORER: Nor do we need one in order to --

MEMBER CARABELLO: Exactly.

CHAIRMAN BORER: Yes. Okay. 2.2. "Available controlled experience with the sustained-release formulation and trials of duration greater than one week." Now, you know, this may be a larger issue. Steve, as the Committee reviewer, do you want to approach that?

MEMBER NISSEN: You know, I -- sorry. I

don't have a whole lot of trouble with this. I mean, I guess if I were to characterize my response to this Question 2 overall, is I think the evidence for efficacy is pretty compelling. I think it only becomes an issue when one gets to 2.3. where you start talking about the dose-response curve. I mean, you know, I doubt if there is anybody at this table, if there is they should speak up, that doubts that the drug is an efficacious anti-anginal of comparable efficacy to other drugs, you know, within the group of anti-anginals.

Now, it's only a question of whether we have enough information on the sustained-release formulation to know exactly how to label the product for our colleagues, you know, to use to know exactly how to dose it. And that is where I sort of get a little bit less clear, but I don't think I need much more efficacy information on longer term exposure.

CHAIRMAN BORER: Okay. You know, it's impossible to divorce efficacy from safety, but let me ask you to respond to this. The standard for approval of drugs is the availability of substantial evidence

from well-controlled trials, which is interpreted as meaning more than one. Here we have two pivotal trials. One of them, CARISA, clearly shows that the drug is effective. Forget about dose-response for a minute. The other one, MARISA, may not meet that standard or it may, and we have to hear about that. If it does, does it meet the standard that we would set for a second piece of evidence favoring efficacy sufficiently, so that we can construct a reasonable benefit to risk relation given the safety database we have? So I would ask you to respond to that.

MEMBER NISSEN: Tough question. I mean, I think that you're right. You can't divorce the two. And, you know, what's actually interesting is I came in here less convinced than I have been during the course of the meeting. I got to give the sponsor a lot of credit for having put on, I think, a very convincing case both for efficacy and for relative safety.

And so what happened to me here today is that I came in with somewhat higher levels of concerns about safety and somewhat higher levels of concern

about efficacy and I got reassured on both sides. And so if you look at the equation, you know, I don't think that this drug is very far away from having a commencing case that efficacy is good for the safety concerns that we have.

I do think there are a lot of issues, a lot of little issues here on dose-response and on concomitant meds and whether it actually works, you know, in patients that are maximally treated and all those things we raised. But, you know, I don't think the efficacy comparison to safety is very far out of balance for what I would expect to see in an approvable drug. So I think it's very close.

CHAIRMAN BORER: Does everybody else agree with that or are there any other opinions? Okay. 2.3. "Available information on the dose-response relationship for exercise tolerance." We have talked a little bit about dose-response. We have heard some opinions. Does anyone have anything else to say about the adequacy of the description of dose-response?

DR. PRITCHETT: I'll just make a summary remark. I think that there are enough data now

available to pick the doses, the marketable doses, without additional studies.

CHAIRMAN BORER: And what would they be?

DR. PRITCHETT: Well, I think -- I don't feel strongly. I think it could be, the upper dose could either be 1000 or 750, you know, and it could either be 375 or 500. The sponsor, I think, has proposed, you know, 500, 1000 and I would probably go with their recommendation, but if people were anxious and wanted to ratchet things down and say well, you know, I want to move it down a notch, you know, I think you could do that and if that provides reassuring safety information that made more people comfortable, I wouldn't object terribly to that.

CHAIRMAN BORER: Doug?

DR. THROCKMORTON: I'm interested in a little more conversation about that from other members of the Committee, please.

CHAIRMAN BORER: Do we have any other comments? Beverly?

UNIDENTIFIED SPEAKER: Sure. You go first.

MEMBER LORELL: Let me just reiterate. I am concerned that we don't have, I think, any efficacy data of 500 milligrams, the lower dose, added on to any anti-anginal. And I would like to echo Dr. Cunningham's concern that for approval in a United States population, I think we have strong efficacy data that this works in white men, and I think we don't have the kind of sense that was talked about earlier. I think all of us probably feel for that population, this balance of safety, efficacy feels much better than it did coming in this morning.

I'm not sure I feel that about black Americans. We have a very dramatic example last year of a very interesting antihypertensive agent whose overall safety profile and efficacy looked pretty reasonable, except for a group and that group happened to be black Americans. So I would welcome some other thoughts about that.

CHAIRMAN BORER: Let me ask you further. I mean, the issue of whether 500 works on top of something else or not would be really important only if you had particular safety concerns, I'm going to

suggest, because if not, someone could try it and see and if it works, it works and if it doesn't, it doesn't. And if it doesn't, you can push up the dose a little bit. So I don't have a concern about that absent some issue that we may be causing a safety problem here, and this is a low dose and what have you. I mean, how would you respond to that?

MEMBER LORELL: I guess my concern would be I would be encouraged by even a modest data set showing efficacy at 500 milligrams on top of something. I mean, I think if there is no evidence of efficacy in that setting, we're not proposing this as a monotherapy, a new drug for isolated use in angina, then it seems to me that some modicum of data would be helpful. I think the issue about the black American population and the risk balance of efficacy and safety is a whole different issue.

CHAIRMAN BORER: Alan?

MEMBER HIRSCH: Let me just accentuate that. I mean, there is many ways of picking a dose-response and, you know, the physician in practice can do that. If there is no safety concerns, I don't

think there is any essential reason we have to worry about the 500 milligram dose. The sponsor can do it by looking at their experience with the efficacy data and adverse events.

But for the sake of the Panel, in my opinion, I also was intrigued by -- it seems to me from CARISA and MARISA, you get most of your bang for your buck somewhere between the 500 and maybe 750 dose if you measure the treadmill time and potentially, as well, if you look at use of nitroglycerin and report of angina. And yet, I can't really say that with any sense of definitiveness, because I'm not quite sure I have seen enough data at 500.

If I were concerned, it's the bait that I think Bob wanted us to take earlier and I didn't take it, that they wanted to build insurance for safety, I'm not sure we need that. But if we needed that, I would expand the 500 milligram database also adding populations, and have a much potentially more tolerable and safer compound that would give syncope-free, QT interval-neutral angina relief.

CHAIRMAN BORER: Steve?

MEMBER NISSEN: Would we even have this conversation if in CARISA the 750 and 1000 milligrams showed even a numerical difference? I mean, the problem we have is that they were spot on, as I recall, that basically, you know, the effect on exercise time for 750 and 1000 was indistinguishable, and so we're left with a vacuum of information and that creates, I'm sure for Doug, some problems that would not be there if you saw stepwise as you did in MARISA, a stepwise increase in efficacy as you went from dose to dose.

Now, we know all the reasons why that occurred, but so now the question is would it be helpful to have more information around what that relationship looks like in the population most likely to be treated, which is a population already on some anti-anginal agents where this is an add-on? Would it make a difference if we really had better information? I think the answer is it would.

CHAIRMAN BORER: Okay. Doug?

DR. THROCKMORTON: Yes. Just sort of by historical perspective for something, I mean, the

rationale has been to make sure the low dose that's approved has some efficacy as you said, Steve, that clearly there is no advantage to approving a dose that doesn't work, then obviously you could only take on safety risk. And so it is sort of a question of whether or not you're convinced that you know enough about the additive effects of this when used concomitantly, maybe from the higher doses something like that, that you don't need that information. Maybe 500 was robust enough that you're willing to believe that you wouldn't have lost all of that effect even if you had concomitant medications.

But then routinely, we sort of get criticized for not identifying appropriately the dosing and labeling, which is actually the additional part of requirement for drug approval, is adequate labeling for safe and effective uses is sort of the thing that we have to do here. So it is a question of can you describe to a practitioner how to use the product?

Again, there are other small differences. There are differences as far as how people got to the

upper doses. In some studies, the sponsor suggested a titration scheme. I'm not sure that we have data precisely matching that titration scheme. Does that matter to the Panel? Is that a thing that you might see as a liability, that you would like to understand what happens when you start at 500 and move through 750 and go to 1000 or you're prepared to believe that you would receive the same effect?

MEMBER CARABELLO: It's just that the drug levels seem to be very sporadic and unpredictable among individuals, so that even the 375 dose is likely to be efficacious in some people. So I think it's very hard to predict other than to start low and go slow, how it's going to affect individuals.

CHAIRMAN BORER: If this drug isn't going to be labeled for monotherapy, which as I understand is not what's being asked for, what is being asked for is administration in people for whom current anti-anginal therapy is not providing adequate relief, then, you know, I think you do have to know that it's going to give some additional benefit, which is the point that Beverly is making.

But having said that, I really don't care whether I know that from a high dose, and prudence tells me I can start at a low dose, which I know may be effective in some people and studies in which monotherapy was employed, I wouldn't care. I would titrate up, because it's prudent. And if I didn't have a safety concern, I really wouldn't be worried about doing that. Now, if I did have a safety concern, I would have a safety concern throughout the entire dose range. But to answer specifically your question, I don't care that they didn't study the titration scheme.

2.4. "Effects of ranolazine on hemodynamic parameters, vital signs, rate-pressure product," etcetera. Well, we have talked a little bit about that, but, Tom, can I ask you to respond to that, because I think this is specifically relevant to the particular safety issue you were raising, even though it's being raised in the context here of efficacy.

MEMBER PICKERING: Yes. I guess the concern again is this issue of whether it unpredictably lowers blood pressure. I mean, we have

heard that in large doses in young people it may do this. In older people, there is the syncope, but we haven't really had much in the way of systematic blood pressure data in the old people, except during the stress testing. So I think this is something where it would be helpful to have more systematic blood pressures both lying and standing, I might add.

CHAIRMAN BORER: I would add, and then we'll go on to Paul, that the issue that I think Tom has raised and is continuing to raise is one of safety and predictability of a drop in blood pressure. In terms of specifically buttressing efficacy with blood pressure and rate-pressure product, I personally don't think that that's an issue. If the drug prevents angina and does so with evidence of reduction in ischemia, so that it's not a safety concern, that is the patient isn't masking ischemia and going onto a potentially dangerous level of exercise, then I don't really care what it does to rate-pressure product and to blood pressure. As a safety issue though, the predictability and the potential for syncope and whatever, that would be an issue for me. Paul?

MEMBER ARMSTRONG: Jeff, knowing what I know, if I were prescribing this to a 78 year-old in my practice, I would certainly check fastidiously for postural hypotension before I prescribed it and I'm not clear. I presume all the blood pressures we're seeing, except for the IV study, were standing blood pressures, and that we have no information on the effect on posturally modulated blood pressure, and I think this is a good point relative to the safe application and the issue of syncope, which is on our minds, and I think Tom has made some effective points that I agree with in the older population. So it might be worth pausing on that point.

CHAIRMAN BORER: Just a yes or no. Do you have systematic data on lying and --

DR. WOLFF: Yes. Yes, we do.

CHAIRMAN BORER: Okay. Just in a short response, please.

DR. WOLFF: There is little change seen in the postural change in blood pressure until we do get up to doses above 1000 milligrams twice a day. And then in the healthy volunteers we do see, and I did

show in response to a question, some data on the postural change. It's about 8 or 10 millimeters of mercury when you're at 1500 and 2000 milligrams twice a day, both of which are doses beyond which what we think should be used. But at 500, 750 and 1000, there is very little change. I don't think we have that tabulated. The best data comes from the SR studies.

CHAIRMAN BORER: Is that responsive to the point you were making, Paul?

MEMBER ARMSTRONG: Yes, I think it is. I just would like to have seen it in the elderly or in the population that might be at risk of syncope, but it sounds as though there might be something there worth looking at a little more carefully and worth pursuing.

MEMBER PICKERING: I wasn't sure. Do they have data in the patients, because, you know, young people have good bare receptive reflexes and they can adjust. Older patients can't.

CHAIRMAN BORER: Andy?

DR. WOLFF: Yes.

CHAIRMAN BORER: I'm sorry. Repeat the

question, Tom.

MEMBER PICKERING: Do you have postural blood pressure data in the patient population as opposed to the young, healthy volunteers?

DR. WOLFF: We don't have anything currently summarized on slides that we can show, but we did measure the data in MARISA and CARISA, so there are supine and standing measurements. They are not remarkably different from what we saw in the healthy volunteers. I'm sorry I don't have it to present.

CHAIRMAN BORER: Okay. 2.5. "The magnitude of the effect of ranolazine on exercise tolerance." We have heard that the magnitude on treadmill exercise tolerance is, approximately, in the range of what we have seen with other anti-anginal drugs. Is anybody bothered by that? Do we need more efficacy data because of that?

DR. THROCKMORTON: And it could go the other way. I mean, any one of these could be so overwhelming, the effect that was seen was so remarkable as to obviate the need for additional information in some sense or the other. I mean, you

could potentially look at them as good things, too, I mean, more than usually good things.

CHAIRMAN BORER: Did anybody look at it in a more than unusually good thing or is that as an inadequacy in the data set? I'm not seeing any responses. I think nobody thinks that's a showstopper. 2.6 "Accumulated data on the use of ranolazine together with other anti-anginals." And we have had several comments about that, about the possible inadequacy of that information.

Beverly, do you want to make a summary statement about that, about the accumulated data on the use of ranolazine together with other anti-anginals?

MEMBER LORELL: Yes. I think this is a point we have discussed at some depth. I take Steve's point earlier today, particularly in light of the issue of syncope, that it would have been desirable or would be desirable to have more data on the use of the drug over a dose range with long-acting nitrates. So I see that as a bit of a gap in the database.

CHAIRMAN BORER: How about with beta

blockers? I mean, again, I think the requested indication, and correct me if I'm wrong, but the requested indication is to give this drug on top of other drugs and not as monotherapy, and if that's true, do we have enough information to say that that's a reasonable recommendation if the background is beta blocker, for example?

DR. THROCKMORTON: Yes. Sorry. There is even a bit more than that. I mean, the language could say one of two things. Either like most antihypertensives, use in concomitant with other antihypertensive therapy or you could say we work in patients that are resistant to other therapies, the bepridil sort of example, and the latter typically has sort of required studies that have studied patients resistant to maximal approved or tolerated doses.

The sponsors made an argument that they have similar evidence from the accumulated exposure data they have from the variety of studies that they have. And so part of this is a question of is that convincing to you or if they were seeking a claim for treatment in resistant populations, treatment in

patients who weren't otherwise responsive to therapies that, in fact, additional data, additional formal studies might be needed.

MEMBER LORELL: I think those are two quite different questions. I think for the first question as an add-on to background therapy, the data set we have is close with the exception of the gap of long-acting nitrates, as well as perhaps data in the population I mentioned earlier of black Americans for whom we have virtually no data. On the other hand, I would argue that we don't have sufficient data here at all to tell doctors how to use this drug in a resistant population, because I don't think that is who has been studied here.

CHAIRMAN BORER: Steve?

MEMBER NISSEN: Yes. I was also, you know, bothered by that because, in fact, that is how the drug is most likely to, at least initially, be used in people who are in maximal therapy or intolerant of increases in therapy. And so, you know, 50 milligrams a day of atenolol is not maximum therapy nor is 180 milligrams of diltiazem. And so to me, it

would be useful in labeling, but also to clinicians who want to use the drug, to find out what happens if you take one, two or more classes of anti-anginal agents, push them to levels that are fully efficacious, you can try to get people up to maximal doses, and if they still have angina, then you add this drug on.

And if you could show that, then I would urge the FDA to give you a label of showing efficacy in patients who are maximally treated with other anti-anginal agents, which I think would be a very valuable label for you to have and for me as a clinician, it would be a very valuable therapeutic indication, because those are the people we really need help with, are the people we can't make better. If I can make them better by taking their dose of atenolol from 50 to 100 milligrams, I'm going to do that before I'm going to add another agent in, but I don't know that. I don't have any information about that at this point.

MEMBER HIRSCH: Just being clear, that's exactly what we don't know and that's likely a

population for which the drug will be used. So exactly, for the two and three sort of drug using, well, anti-anginal medication using patient with angina, we don't really know if there is superimposed efficacy. There may be a plateau beyond which you don't get additional benefit, and that also hasn't been well-examined.

I want to also share the concern, I think, that both Tom and Beverly had mentioned. I still consider the syncope issue to be potentially concerning in this particular population that will be elderly and using between five and seven global medications. I actually think there has been a wonderful database. I think this has actually been a generally well-tolerated drug, which will be used, but not having data with superimposed nitrates in a potentially syncope prone population, I think, is a concern. I would have liked to have seen that filled in.

CHAIRMAN BORER: Blase?

MEMBER CARABELLO: Yes. I think we couldn't possibly recommend it for patients on maximum

therapy, because we don't have any -- we could really be covered with mud if we did that. We don't have any idea that those patients would get any better on this agent. So I think that in that group of patients, we just haven't seen those data. The people who did have syncope, two thirds of them were on one or more vasoactive agents besides ranolazine. So I think that certainly can be added into the label.

CHAIRMAN BORER: Okay. 2.7. "The effects of ranolazine on 'hard' clinical outcomes." Let me make a statement and, again, just respond if you disagree. This is an efficacy question. I don't think it's relevant here. This is the drug is being proposed as an anti-anginal. Nobody has suggested it prevented death or myocardial infarction. And on the safety side, which is not this question, there were relatively few data, but there was certainly nothing that suggested a major red flag and I don't think we have a reason to be concerned about that any further. Doug?

DR. THROCKMORTON: And just on the other side, you saw nothing here that made you -- no

efficacy here that suggested to you a benefit above the sort of symptomatic claims that we have been discussing?

CHAIRMAN BORER: No. It hasn't been studied and there are no data to inform us about that. Question 3 "What additional data, if any, are needed for ranolazine to obtain a claim for use in an unrestricted population with angina?" I have a feeling that we have given you a great deal of information about that.

DR. THROCKMORTON: Yes, but this is an important question to us, Jeff. In this particular case, I guess I'm going to ask that each member be asked to discuss this question to the extent that they feel necessary. Again, it's sort of a regulator's sort of question. The sponsor is interested in an approval, obviously, and the approval could be of different flavors, if you will, and the flavors are outlined in the bullets, sorry, in the numbers and in the bullets there, and the Agency is interested in some discussion that has gone already, but discussion from each of the members about whether the current

data set sort of meet any of those standards, whether they view that there is sufficient data available to give one of those claims or the other. And if not, what additional data would be needed? Again, we have had some conversation already to support one or more of these particular claims. Is that clear?

CHAIRMAN BORER: Yes.

DR. THROCKMORTON: But I would ask that each of the members be asked to give an opportunity to speak.

CHAIRMAN BORER: Okay. Why don't we take Question 3 in its entirety and everyone can give whatever opinions he or she thinks are appropriate. We'll start with Steve, who is the Committee reviewer, and go around the table that way. Steve?

MEMBER NISSEN: Very tough question, Doug, probably the crux of it all, because it really all depends on to what extent you're worried about the QTc prolongation effect. If it's really a non-issue, then you have another class of drugs that's arguably equally effective to the other classes and, therefore, should be able to be used in an unrestricted

population. The difficulty is we have got, you know, only about 1,700 patient-years of exposure. We have preclinical data, which is interesting, but we don't have a lot of precedent for knowing what that means, so that there are several strategies for dealing with this.

The problem is I don't see any way out of the box, because if you say well, to use it in an unrestricted population, you have got to have very good evidence that you're not going to cause torsade. Well, you are not going to find that out until the drug has been out there for a fair amount of time. And so if that's the standard you want to apply, you're not going to be able to apply it premarketing. There is no way to know that.

DR. THROCKMORTON: Okay. That might be true. You can think of lots of sort of possible ways out of the box, I guess, but I guess I'll just provide one and the one possibility that has been discussed, obviously, is a resistant population claim that would allow marketing and then follow-up. You know, you would follow and see and, at some point in the future,

the claim would be expanded. That's a fairly standard way for the Agency to handle uncertainty, let's say, or a place where you have got to benefit a resistant population that you view or might be viewed as offsetting this potential safety, and you get additional information that would allow you to broaden it later, I guess. That's at least one possible way.

There may be other ways, the proposal the sponsor has made about an outcome study. Is that a thing that moves you? I mean, there are other sort of strategies that you could think about.

MEMBER NISSEN: I don't think there are, you know, and the real -- for me there are not, and the real question is does the level of concern about QTc rise to the level where you would want to restrict this drug to a resistant population, and I am pretty much on the border about that. I mean, I know the problem is there. I am reassured by the preclinical data.

You could argue that letting the drug out there in an unrestricted population is probably the fastest way to find out. You know, you get enough

exposure, you're going to find out pretty quickly whether there's a problem or not, and I know that's not something a regulator would like, but, you know.

DR. THROCKMORTON: Could you name who would like that just so I could talk with them?

MEMBER NISSEN: Yes. I don't know. You know, I guess the argument for giving it to a restricted population only is that we do have other anti-anginals. If we didn't, I think it would be a harder case. And so I think you could arguably say let's limit it to a very restricted population, get it out there and if we don't see any additional safety concerns emerge, take away that restriction at some time in the future. I just wouldn't want that to be years and years and years if the drug were really effective and safe.

DR. THROCKMORTON: So just to complete that thought, you previously said that if a resistant population was what the sponsor was looking for, the available data were not sufficient for you, so then would you -- again, without putting words into your mouth, can you tell me what additional data you would

want?

MEMBER NISSEN: Yes.

DR. THROCKMORTON: And that goes to 3.2.1.

MEMBER NISSEN: Yes. I mean, I would do a study in patients that are maximally treated with conventional anti-anginal agents or intolerable of them, and demonstrate both safety and efficacy in that population. I think that would be a very useful, you know, piece of data to allow you to say this drug works in a resistant population.

So now, you know, how many drugs and all of that is, you know, hard to say, because it's going to be very tricky, because sometimes if you push the beta blocker up you get certain dose limiting toxicities. You push up nitrates, you push up calcium channel blockers, some patients will reach maximum tolerance with one drug. Some will reach it with two and some will reach it with three. So I can't write the script for that very easily. Although, somebody would obviously have to be able to do that.

DR. THROCKMORTON: No, I would like you to try for us and there is two things. Remember, you

helped write the script for omapatrilat.

MEMBER NISSEN: Yes.

DR. THROCKMORTON: So you do have, you know, sort of experience with the writing of these sorts of things. Two sort of possible things. Typically, what we have told sponsors is in anti-anginals, although not in resistant antihypertensive populations, is that demonstrating benefit on top of one anti-anginal at maximal labeled or tolerated dose, that was sufficient to sort of demonstrate a resistant population claim.

Now, you have raised another possibility. Well, so I don't tolerate nitrates very well, but maybe I tolerate, you know, calcium channel blockers, you know, without any edema, without any trouble, so if the one drug rule was what you were interested in, would I be obligated, would the sponsor be obligated to switch between, say, the three typically ordered anti-anginal classes before saying intolerance or is an arbitrary choice of one or the other?

Although, I mean, you can imagine some populations are almost predictably less tolerant of

one class or the other. And then the add-on, is the advice we have been giving people reasonable, that is a single drug sufficient to test the question of resistance or should we be asking sponsors to look for -- put people on more than one drug? Again, as you say, with the uncertainty of this agent, you have two other drugs, three other classes out there. So it's a complicated question, but it does matter as far as sort of development.

MEMBER NISSEN: It's much harder, Doug, here, because the dose limiting toxicities for each of these three agents that are currently available is different. You know, some patients you give a smidgen of isosorbide dinitrate to and they get the worst headache of their life and they say don't ever give that drug to me again, I don't want to ever see you again, you know, and other people who get pretty profound responses to beta blockers. So you know, it's just not that simple.

When we talked about omapatrilat we got blood pressure, right? And we said all right, you throw one drug after another at them and if their

blood pressure is still above X, Y or Z, then they are resistant. I don't think with anti-anginals it's nearly that simple to design a trial to actually do that. So I'm not sure I can write that script as easily for you.

CHAIRMAN BORER: Alan?

MEMBER HIRSCH: I wish you had gone the other way around the table. It is very challenging. I'm not going to have an answer for this one. Though I have been a critical voice, I find the development program to have been enticing and it has actually been convincing to me that we have an effective agent that probably could be useful in either a resistant population or in a general population in individuals with angina.

Let me first start where Steve left us. I don't think it's easy to define, though I called for it, for a study that looks for one, two and three drug resistance. Though I would like to see it, I would like to see it more in a broad based, large population, sort of an interventional trial of individuals with angina where that naturally might be

part of the background treatment. And then I would post hoc evaluate that. I think it's very hard to pre hoc define resistance. So I'm not sure.

Alternatively, maybe just to go the other direction to an unrestricted population, one more pivotal trial. I think that if we sort of are reassured. I have been reassured by the QT prolongation, torsade issues a bit to this point. One could jettison the approach, at this point, to look for resistance and attempt to gain approval for a first line therapy.

CHAIRMAN BORER: Who should be -- what population should be studied in that trial?

MEMBER HIRSCH: That would be individuals with angina.

CHAIRMAN BORER: Okay. So you --

MEMBER HIRSCH: Broad based population.

CHAIRMAN BORER: You have no concerns about sub-populations that haven't been studied?

MEMBER HIRSCH: They would be answered, as sort of Bev called earlier, by their inclusion in the next trial.

CHAIRMAN BORER: Tom?

MEMBER PICKERING: Well, this is being compared against three classes of anti-anginal agents, all of which are effective and on all of which we have huge amounts of long-term data, so we know they are safe. In the case of beta blockers, they do other good things. So I would be very concerned about its unrestricted use. I think potentially it does have a place in patients who have failed or who are still symptomatic while being treated with the three conventional agents, but I don't think -- I mean, we haven't heard anything about how effective it is on patients already taking long-acting nitrates.

So I personally would like to see more data in patients who have been tried on maximal doses of the more conventional agents to see if this really does have a beneficial effect, which I would define not only by doing treadmill tests, but also by talking to the patient, which nobody seems to have done.

CHAIRMAN BORER: Beverly?

DR. THROCKMORTON: Sorry. One drug, two drugs for your resistant population?

MEMBER PICKERING: Well, I think they should have been exposed to three drugs. I mean, maybe not. They couldn't necessarily tolerate them all, but I think that would be the conventional way to try those three other drugs first.

MEMBER HIRSCH: Can I ask him to follow-up? Do you mean this in a deliberate, prospective manner or in a more broad, "real-world" population where some will be treated with one, two or three?

MEMBER PICKERING: I'm not sure I'm going to design the study, but I do think the question has not adequately been answered whether the patients that we have heard about could have been controlled by increasing the dose, say, of the beta blocker or the amlodipine or the diltiazem and the nitrate stories.

CHAIRMAN BORER: Beverly?

MEMBER LORELL: I think the safety issues that we have discussed today have been modified by the beautiful preclinical data we heard, but have not completely gone away. To my mind, the preclinical data is elegant and is hypothesis generating, but doesn't allow us to say with surety to any of our

patients that there is no increased risk of torsade or excess syncope with this agent compared to other available drugs.

That being said, I personally would be very comfortable with what I would think would be a very modest label of restriction. To me it's formidable to think about how one might do this complex matrix of perhaps patients who remain symptomatic despite treatment on one or more other anti-anginal drugs. Remember that what will inform doctors in the "real-world" about how to use this agent is a single trial, which is CARISA, and that's what that trial did.

However, not to beat a point, but I would like to see for its use in the United States a modest trial with that kind of permissive restriction, if you would, in black Americans, because otherwise, I think we don't have either safety or efficacy data on a big chunk of the United States population who has refractory angina or difficult-to-manage angina.

CHAIRMAN BORER: Dr. Knapka?

DR. KNAPKA: Yes, thank you. Well, first

I want to commend the sponsor. I was very impressed with the data. Usually, those of you who know me, I am real critical of statistics and I didn't have anything to really criticize this time. As I said before, I think certainly from a patient's perspective, and I have been one that had angina, and I do know when the pain goes away you feel better, Tom.

But I would probably vote that there be some marketing of this drug to a restricted population, which we know, and at the same time probably be another clinical trial, another trial done that includes actually a sample that represents the population where the drug is going to be sold. Now, that may mean folks taking two to three of the drugs, different ethnic backgrounds, races, gender, but I just think the weakest point in the core study is that the sample used does not represent the American population.

DR. THROCKMORTON: Sorry. Just to clarify. So from your perspective, you believe there is currently available data sufficient to give the

sponsor a claim in a resistant population or do you think that additional data are required before that would be possible?

DR. KNAPKA: I think they should be done concurrently. I think that --

DR. THROCKMORTON: Right. So "concurrently" means available data are sufficient to allow approval in a resistant population?

DR. KNAPKA: Right, and then do this other study.

DR. THROCKMORTON: Okay.

CHAIRMAN BORER: Blase?

MEMBER CARABELLO: I have been persuaded that this is a safe, effective agent. I mean, we say that the current agents that we have available are safe. That is only because we have learned how to use them. Certainly, we were all there when beta blockers almost killed a bunch of folks or when calcium channel blockers almost did the same thing. We have simply learned how to use those drugs in a safe fashion.

CHAIRMAN BORER: Steve wasn't here. He wasn't born yet.

MEMBER CARABELLO: Well, I know, he wasn't born yet, but that doesn't mean those specific agents were any safer than this one. We simply learned how to use them safely. I don't think we have any evidence that this agent is going to be any more effective in a resistant population, depending on how you define that, and I don't see limiting it to use there. In fact, I think that's the area where we know the least about its efficacy. So I wouldn't get excited about calling it for use in a resistant population.

I do think Beverly's concern is one we can't gloss over. It has been used in preciously few black Americans, and I don't know how you get around that. We just don't know what its safety is there, but I guess I would vote for, you know, it's unrestricted use. And I don't know, have we ever labeled an agent? We label agents as not proven safe in pregnant women, etcetera, etcetera. Have we ever labeled an agent as not proven safe in a race or in another category of patients?

DR. THROCKMORTON: In fact, we're fairly

standard issue asked to reflect the available data at a minimum, which is so in this case it would be -- well, I mean, so you would look at the data and say we don't have any information as to safety and efficacy, whatever that is, unless you thought there was a signal that, in fact, there was diminished efficacy or safety concerns, something like that, like the LIFE trial, like might be the case for women here or something like that.

So just to be clear, your recommendation is approval in an unrestricted population based on the available data?

MEMBER CARABELLO: Yes, with the appropriate labeling caveat.

DR. THROCKMORTON: Right.

MEMBER CARABELLO: About vasoactive agents, etcetera, etcetera.

DR. THROCKMORTON: Sorry. Vasoactive agents?

MEMBER CARABELLO: Well, I mean, I think you would urge caution in patients taking other or taking vasoactive agents since that's where two thirds

of the syncope occur.

DR. THROCKMORTON: I see. Okay.

CHAIRMAN BORER: Ed?

DR. PRITCHETT: Well, as a principal of drug labeling, my sort of first principle is that the drug should be labeled for the population that was included in the clinical trials, and I think so, and I'm actually quite persuaded by the efficacy and safety data that we have seen here today. And so the population that I like would be the CARISA population, you know, where I think we have the most data. You know, and that's a population that included people who were on, you know, one other drug at least. It excluded patients with Class III and Class IV angina, you know, but I would craft, you know, the target population around the CARISA population.

I think that the concept of defining a resistant population and doing some kind of study in that population or labeling that population is one of those ideas where the devil is really in the details, and I think that to go out and try and write a protocol that recruited patients with resistant

something or patients who were on maximally tolerated something, I think would be very difficult. And in addition to that, I think if you took that protocol around to angina clinics, that all the investigators would say I got thousands of those patients in my clinic, and then when you gave them the protocol they wouldn't be able to recruit any of them. It looks like a very difficult concept.

So in addition to that, I am troubled by the fact, by the notion of saying that based on the current data set that we should restrict the drug to use in some population that essentially wasn't studied. So I am much more comfortable with saying I like the CARISA population as the population.

DR. THROCKMORTON: Okay. So let me just ask you a little more about that. The basis of that conclusion would be that you have adequate safety information?

DR. PRITCHETT: Yes.

DR. THROCKMORTON: That the reason to choose a resistant population is that that's a benefit above and beyond a general population. It's a therapy

when no other therapies are available that gives you additional ability to tolerate uncertainty and safety. I just want to make sure that that's the basis for your thinking.

DR. PRITCHETT: Well, no, what I'm saying is that I am uncomfortable with saying here is a new drug and let's use it in a resistant population when, in fact, it hasn't been tested in a resistant population.

DR. THROCKMORTON: Right, and I know that's right.

DR. PRITCHETT: At least about efficacy and safety in a resistant population.

DR. THROCKMORTON: Right. So I hear that loud and clear. You don't believe that efficacy has been demonstrated in a resistant population. But again, that the trials have been done, of course, is true. We have done resistant trials, resistant population trials. You know, sort of without any difficulty, obviously, bepridil was able to do theirs with -- I mean, that's not an insoluble problem if you believe it's necessary, and so it's back to that

necessary part. Your assertion, it's difficult, is not the same thing as saying and it's necessary? So you're saying it's not necessary?

DR. PRITCHETT: It's not necessary.

DR. THROCKMORTON: Okay.

DR. PRITCHETT: Okay. I believe it's not necessary.

CHAIRMAN BORER: Ron?

MEMBER PORTMAN: I agree with Ed in large part. First, I again want to compliment the sponsors on a terrific job of presenting their data. I am convinced, as a nephrologist, of the effectiveness of the drug in the population studied. I also think that the safety is reasonable, particularly in the lower maximal dose, and I would certainly favor that. I mean, clinicians will raise the dose if they can and if they would see that it's going to be more effective on their own, but if you look at the data, there is at least a twofold increase in some of the side effects when you get to 1000 compared to 750 where the efficacy, you know, seems to be pretty good at that level.

So I would label this, I think, for a resistant group, but again, similar to the CARISA Study. If we were looking at the bullets under 3.2.1., I think the first bullet and the third bullet look reasonable to me. For those who are symptomatic maximally tolerated, of course, we haven't studied maximally tolerated, of one other anginal drug or in those patients where just for some other reason, those other drugs can't be used, and I think that would be reasonable. The second bullet would require further study.

So I think, again, concomitantly we could have that approval, but I still urge, as Beverly has suggested, that we go forward, the company go forward with additional studies, particularly looking at the African-Americans, studying the hepatic group in more detail, the renal group. And whatever they do, I hope the company will look at trough levels on population kinetics, particularly with all the different concomitant medications that can effect 34A, just to see what effect these multi drugs will have on the levels.

CHAIRMAN BORER: Ron, if I understand, you're saying that it's approvable. You believe it's approvable right now for unrestricted use?

MEMBER PORTMAN: No.

CHAIRMAN BORER: No? Okay.

MEMBER PORTMAN: For restricted use.

CHAIRMAN BORER: It's approvable for restricted use?

MEMBER PORTMAN: Right.

DR. THROCKMORTON: Ron, say more about the third bullet. How would you identify those patients? I'm asking that only because --

MEMBER PORTMAN: Yes.

DR. THROCKMORTON: -- we haven't had a chance to talk a lot about that.

MEMBER PORTMAN: It's fine. I mean, look, to be honest, it's imaginary for me. I mean, I don't treat patients with angina. Okay. But, you know, just from a logic sense, I mean, I could see that you could come up with a patient, you know, who for some reason can't take a beta blocker, can't take a calcium channel blocker or not higher doses.

DR. THROCKMORTON: Right.

MEMBER PORTMAN: And thus --

DR. THROCKMORTON: The sponsor has made a number of proposals in that.

MEMBER PORTMAN: Right.

DR. THROCKMORTON: Along those lines, and I wanted to ask one, if you found that credible, and then I will return to something that Bob Temple asked earlier, argued that some blood pressures, some individuals' resting blood pressures might be so low that let's suppose that the other blood pressure lowering agents that were also anti-anginals, you wouldn't want to try that. I wondered if you had a cutpoint in mind in that regard or if anyone had a cutpoint in mind in that regard.

The question is whether it's an a priori demographic, a bench mark, or whether it needs individual determination. So if the sponsors propose that the bench mark of anyone below, well, I don't want to get it wrong, correct, 60 beats per minute would be at risk for the diltiazem, that no reasonable physician would ever give them diltiazem because of

the concerns over the AV block, that that identifies a population that shouldn't get diltiazem. So it's not that they are not resistant. It's just that they shouldn't get it. I mean, I'm seeing a nodding head, so I'm taking that resonates with you.

MEMBER PORTMAN: Yes, it does, it does. And I think it's obvious that it's very complicated not just with other levels and all the different concomitant medications, but, you know, even in the -- we're talking about lowering blood pressure and yet, Paul was showing me that in the renal group, the diastolic blood pressure went up 10 millimeters of mercury. So I think it's a very complex issue.

DR. THROCKMORTON: Right. And certainly, it's a complicated issue, excuse me, given the variability of the patients.

MEMBER PORTMAN: Right.

DR. THROCKMORTON: Pharmacokinetics and things like that, but you believe, again, a sort of line in the sand approach is something that would be approachable here?

MEMBER PORTMAN: I do, yes.

DR. THROCKMORTON: Steve, I'm sorry, I see other --

MEMBER NISSEN: You know, it just isn't that easy, Doug, because we see patients, sometimes heart failure patients, I know Bev probably sees them, that walk around with blood pressures under 100 that are asymptomatic and that you could give them nitrates and you wouldn't have any trouble at all. I mean, and we actually do sometimes push beta blockers in those patients and we work our way up to high doses sometimes over a period of time.

And so the notion that there is some line in the sand that defines such patients is not realistic. That is why this is so hard, is that it is really a difficult judgment about what is a medically refractory patient. In this particular arena, it's extremely difficult, and so it's very hard for me to actually answer that question for you in a way that would allow you to design a trial. I am really struggling with it.

DR. THROCKMORTON: Yes. Well, the bepridil experience was fairly clear cut and, again,

we haven't talked a lot about that. That was patients demonstrated to be resistant to diltiazem, then re-randomized to either diltiazem or to bepridil. Now, that was a superiority trial. Again, that isn't the sort of thing that we would be talking about here, but that was a trial of, I don't know, 50 people or something like that. It was not a huge number. So, I mean, that is at least one way to approach it. But I am interested in more conversation around the sort of other population, this intolerant population, when we get to the end, but let's go to the end of the group here first if we could.

CHAIRMAN BORER: Paul?

MEMBER ARMSTRONG: Starting from 3.2.2. then, I would favor a broader population, more background medical therapy, longer duration and incorporation of silent ischemia with the added benefit of QT being able to be measured on Holters out further. For me approval with limitation to one prior anti-anginal, I actually bring a different approach to this. That is to say, I mean, I think they should all be on beta blockers, and I think many of us translate

the evidence on beta blockers on hard endpoints to the anginal population. So my view would be that that would be a minimum.

Like Blase, I think the calcium antagonists, many of them are not all that safe and there are some problems, but of course if one were concerned about AV block with diltiazem, one would use amlodipine or dihydropyridine, so that the issue of selection, vis-a-vis a calcium antagonist in this situation is moot. But I would certainly be prepared to consider ranolazine in a patient who is on beta blockers and still having angina.

The nitrates have tolerance and windows of vulnerability notwithstanding their venerability, and I do think on the third bullet that there are a significant proportion of patients that either are asthmatic or have significant AV block. The low heart rate at rest again, many of us would put a beta blocker since the exercise heart rate is a far better marker than the resting heart rate of beta blocker. So I think these are complicated issues, but I would make the additional pitch that the patient, unless

intolerant, should be on a beta blocker, and that would be my opinion.

DR. THROCKMORTON: So, Paul, sorry, just to -- if I understand then, you believe additional data are needed in a resistant population, and you have talked now about the way that resistant population looked. Does that capture what you're saying? I just want to make sure I'm not --

MEMBER ARMSTRONG: Well, it was resistant, but also I said broader and also background therapy. So I think to touch on the other --

DR. THROCKMORTON: Issues like what Dr. Pickering and Dr. Lorell raised with nitrates and things like that.

MEMBER ARMSTRONG: Yes, yes.

DR. THROCKMORTON: Okay. And I also heard some sympathy for the intolerant population, but I wasn't sure how well you thought that population or how best to define an intolerant population.

MEMBER ARMSTRONG: I think that you lay out some general parameters. I don't think that you lay out numbers. I think that you say symptomatic

intolerable hypotension or bradycardia and you leave that to the physician and the patient.

DR. THROCKMORTON: Okay.

CHAIRMAN BORER: Paul, just to clarify, I didn't hear. 3.1, you didn't specifically respond. Do you think additional data needed for ranolazine to obtain a claim for use in an unrestricted population and if so, what do they need?

MEMBER ARMSTRONG: I'm sorry, I implied that I thought the label should be in a resistant population that was taking one anti-anginal that was a beta blocker or if intolerant another, and I suggested that the further characterization --

CHAIRMAN BORER: Not if they wanted an unrestricted claim. What kind of data did they need?

MEMBER ARMSTRONG: More patients, longer period of time and broader population and better background therapy.

CHAIRMAN BORER: Susanna?

DR. CUNNINGHAM: Yes, I think the only population currently now that they could be approved for are white males, so I think to be approved --

okay, once again, we're at the same place where we seem to always end up. So I think that's an ongoing problem. I think to get approval we need a representative population that is representative by gender, is representative by ethnicity and that's not just African-American, that is Hispanic and that is Asian-American, Pacific Islander population.

I think the population to be approved should be identical to the population that has angina in the United States. So I think we just need the epidemiology data of who has angina and that's the population we should look at. I think, Tom is right on that we should talk to these patients. It is key that they feel better. If they don't feel better, it's not really getting us very far. So I think that's the other piece. And I will defer to my cardiologist colleagues in terms of other medications.

CHAIRMAN BORER: Okay.

DR. THROCKMORTON: Jeff, sorry, I need to press just a little bit more on this one. I apologize. What I heard around the table and I'll ask for people just to clarify is that at least five of

you saw a way to get -- and oh, you haven't even given yours yet. I better be -- how old are you?

CHAIRMAN BORER: I'm getting older every day. Okay. I was very impressed with the presentation and I'm really much less concerned about the QT issue than I was when I came in or that I might have been. And I agree with Steve that there is no reasonable single study that is going to resolve any lingering concerns, even though I have lingering concerns. So I have some lingering concerns that can't be resolved, but that doesn't mean that the drug can never be approved.

I have a somewhat greater concern about the syncope issue, because I don't quite understand it yet and I don't understand it, particularly. I don't understand how much I should worry, particularly, in the context of nitrates being administered, because we have so little information about that. In addition, although it isn't the show stopper issue specifically for approvability, at the first instance, I am concerned that we don't have sufficient dose-response information to adequately write a label.

But in terms of approval for an unrestricted population, forgetting about all those things, I have to agree with everyone who said that we haven't seen a representative and a varied enough population to give unrestricted approval for this drug. And I think that in order for that to be done, we do need to see some data. It doesn't have to be from a well-controlled trial on angina. It can be from an experience in 50 patients who are on both.

We need some information about the concomitant administration of nitrates and this drug, specifically with reference to what happens to blood pressure, whether any syncope occurs. There just needs to be some experience that is greater than what we have. I think that we need a study that involves women and some representation from sub-populations that are important in the United States numerically, so that we can have some sense that all those groups are reasonably likely to respond to the drug.

And in the context of doing that, I would like to get some more information about those response. So I think that an additional study would

be helpful, would be necessary or additional data would be necessary for approval in an unrestricted population with angina. Along the way, we would get more information, of course, about QTc and torsade, but not enough to resolve that issue. As I've said, however, I don't think that that's a show stopper for any approval.

If one doesn't want to do the additional study that I think is necessary to confirm efficacy and acceptable safety for unrestricted approval, if one didn't want to do that and didn't want to get the additional information about drug combinations and what have you, and one wanted to go the route of a restricted label for a restricted population, then I don't think we have the data to allow us to provide an approval or to write a label for such patients.

And if you ask me what population should be studied, well, I'll tell you what I think could be done and should be done for restricted population. I would say that it is reasonable to study patients who still have angina on a maximally tolerated dose of at least one other anti-anginal drug. It could be more

than one. It could be three. It could be two. It could be one. It doesn't matter to me, because my expectation is that within a study that would be done, the entire range would be involved, that would be my expectation, and that we could look for internal consistency within such a study.

And in that population, I would also allow to be included people who have conditions that would make them necessarily inappropriate candidates for one or another of the current classes of anti-anginal, specifically people with major conduction blocks, patients with asthma, maybe I could add on a few more. So I would be perfectly happy with a relatively heterogenous group to be studied for restricted label with the proviso that there be reasonable consistency in the results in that group for a restricted label, if that's what the sponsor wants.

You know, so I could see a study that could be designed to give approval for restricted labeling. If unrestricted approval is what is wanted, then I would want to see more data the way I've outlined it.

DR. THROCKMORTON: I'm fairly certain unrestricted approval would be what they would be most interested in, and you don't see that as -- you see that as possible is what I'm hearing. Is that right?

CHAIRMAN BORER: I see it as possible, but I would like to see the data that I said should be obtained before I would suggest that that should be done. Okay. Are there any additional questions you want to ask before we get to 4?

DR. THROCKMORTON: I just wanted to ask if anyone wanted to comment about we've had a fair amount of comment about how well people do or do not believe they understand the dose-response of the agent. I don't know if anyone has any need to say anything else. I think we've had a fair discussion about that from the two studies.

CHAIRMAN BORER: What about the issue of duration of controlled exposure? I mean, that came up and, you know, we haven't required long duration, that is longer than the three months controlled exposure. Do you want comments about that?

DR. THROCKMORTON: Well, no, sorry, I

think you're missing -- the thrust of the question is not that. The thrust of the question is you have a single study that exposes patients for more than one week, as far as testing anti-anginal efficacy. Again, that would be short of what we have required in the past for other anti-anginal development projects, at least that I'm familiar with. Maybe there is a good rational for that. It was just a question whether or not you believe we should, in fact, relax that typical requirement.

CHAIRMAN BORER: For a second study?

DR. THROCKMORTON: A second --

CHAIRMAN BORER: Like CARISA?

DR. THROCKMORTON: -- longer study would give you more safety information. It would provide you additional information. I mean, it has to do with all of the stuff we've been talking about, but are you satisfied that one study going longer than a week, in fact, adequately bounders what you need to know about this drug? This is sort of another way of asking the question.

CHAIRMAN BORER: Yes, I would be satisfied

with that. Are there any other responses? Beverly?

MEMBER LORELL: Yes. As I said earlier, I also would be satisfied with that for a restricted population, and I would probably use the word persistently symptomatic as opposed to refractory, which I think has slightly different meanings. But I would not be comfortable seeing this drug for unrestricted use as monotherapy, since we only have one week of experience as monotherapy in a controlled trial at each of the doses. And I don't think one week of experience is sufficient.

CHAIRMAN BORER: Can I just make a point about that? I mean, the current guidelines would allow that. If there is one week and it shows clear effectiveness and you are satisfied with the effectiveness, I don't know if you would be from the data we have here from MARISA, but if you were satisfied with one week of monotherapy placebo-controlled data, if you were, then all the rest of the development program does not have to have prolonged monotherapy. And, in fact, a very reasonable alternative would be to have a placebo-controlled

trial on background therapy that runs for three months. I mean, you could do that.

MEMBER LORELL: Just to restate with the current data, I personally would not be comfortable with unrestricted monotherapy use.

CHAIRMAN BORER: And what would you want in addition?

MEMBER LORELL: I would want to see, I think, some of the parameters, Jeff, that you brought up. I would want to see a longer experience and in a much wider database, more typical of United States anginal population.

CHAIRMAN BORER: Doug, have we exhausted this or do you want deeper probing?

DR. THROCKMORTON: No, I think I have probably heard what I need to hear, unless other people have comments about that. The demographics, I guess, a great number of people have made a lot of different comments again, unless there is things people need to say about that. I probably have heard enough as well.

CHAIRMAN BORER: Okay.

DR. THROCKMORTON: So no, I think, we're quite happy with that.

CHAIRMAN BORER: Let me summarize, because I understand that a short summary is desirable. I believe that what we collectively have said is that, in general with some exceptions, and it's not unanimous, the group would not be happy with approval of this drug for unrestricted use in patients with angina, based on the current data set. That wider experience, perhaps with some longer duration with some associated use with other drugs that are anti-anginal, so at least we have some way of understanding the potential problems, and some more experience to give us a better handle on the magnitude of syncope risk, perhaps that this would be appropriate before considering this drug for unrestricted approval.

That it could be approved with a restricted label only if studies were done, appropriate studies, in a population defined as we have given you some definitions of that could be accepted as being resistant to current therapy or highly likely to be resistant to currently available

therapy. So if an unrestricted label is desired, more data are needed. If a restricted label is desired, more data are needed. I think that's basically what we, as a group, came down to, although there are some variations that you can read in the transcript.

Does everybody subscribe to that? I'll take that as a yes.

DR. THROCKMORTON: My thanks to the Committee for two days of heroic endeavor. The Agency very much appreciates your assistance. Thank you very much.

CHAIRMAN BORER: The meeting is concluded.

(Whereupon, at 4:04 p.m. the meeting was concluded.)