DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

Wednesday, July 9, 2003

8:30 a.m.

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Glenn Braunstein, M.D., Chair
Dornette Spell-LeSane, M.H.A., NP-C, Executive Secretary

Members

Dean Follman, Ph.D.
Lynne L. Levitsky, M.D.
Nelson Watts, M.D.
Paul Woolf, M.D.

Special Government Employee Consultants

Thomas O. Carpenter, M.D.
Jeffrey B. Kopp, M.D.
Charles Hennekens, M.D.
Margaret Wierman, M.D.

ACTING INDUSTRY REPRESENTATIVE

John F. Neylan, M.D.

FDA

Robert Temple, M.D.
Robert Meyer, M.D.
David Orloff, M.D.
Mary Parks, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. BRAUNSTEIN: Welcome to the Food and Drug Administration, Center for Drug Evaluation and Research, Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for July 9, 2003. Today we are going to discuss NDA 21-366, Crestor, rosuvastatin, calcium tablets from AstraZeneca Pharmaceuticals, agent for iPR Pharmaceuticals.

We will start by going around the table and introduce ourselves and tell where we are from and what role we play on the committee. We will start with Dr. Temple.

DR. TEMPLE: I'm Bob Temple. I am Director of the Office of Medical Policy at FDA and I actually direct one of the review divisions, one of the review offices, although it has nothing to do with the one that is operating today.

DR. MEYER: I am Bob Meyer. I am Director of the Office of Drug Evaluation II in CDER.

DR. ORLOFF: David Orloff, Director, Division of Metabolic and Endocrine Drug Products, CDER.

DR. PARKS: Mary Parks, Deputy Division

Director, Metabolic and Endocrine Drug Products, CDER.

DR. CARPENTER: Tom Carpenter. I am a pediatric endocrinologist at Yale University School of Medicine in New Haven. This is my first meeting with you all.

MS. SPEEL-LeSANE: Dornette Spell-LeSane, Executive Secretary for the Committee.

DR. BRAUNSTEIN: Glenn Braunstein, Chairman of Medicine, Cedars-Sinai Medical Center, Chair of the Committee.

DR. WOOLF: Paul Woolf, Chairman of Medicine, Crozer Chester Medical Center, endocrinologist.

DR. HENNEKENS: Charlie Hennekens from Medicine and Epidemiology at the University of Miami. I am a consultant to the committee for this review.

DR. FOLLMAN: I am Dean Follman, Assistant Institute Director for Biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. WATTS: Nelson Watts, an endocrinologist from the University of Cincinnati.

DR. WIERMAN: I am Maggie Wierman, an

endocrinologist from the University of Colorado.

DR. LEVITSKY: I am Lynne Levitsky. I am Chief of Pediatric Endocrinology at Mass General Hospital in Boston.

DR. NEYLAN: John Neylan. I am a nephrologist by training and am Vice President of Clinical Research and Development at Wyeth Research. I serve on this committee as the Acting Industry Representative.

DR. BRAUNSTEIN: Thank you.

We will now have the conflict-of-interest statement read.

Conflict of Interest Statement

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

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

meeting with the following exceptions.

Dr. Glenn Braunstein has been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership in stock in a competitor valued between $5,001 to $25,000. Because this stock interest falls below the de minimis exemption allowed under 5 C.F.R 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

Dr. Thomas Carpenter has been granted a waiver under 18 U.S.C. 208(b)(3) for his membership on a competitor's data safety monitoring board on unrelated matters. He receives less than $10,001 per year.

Dr. Charles Hennekens has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in one of Crestor's competitors valued between $5,001 to $25,000 for ownership of a bond in one of Crestor's competitors valued between $25,001 to $50,000 and for ownership of stock in another of Crestor's competitors valued between $5,001 to $25,000. These investments were

made independent of Dr. Hennekens by Sun Trust Bank which has sole discretionary authority in these matters.

In addition, the 18 U.S.C. 208(b)(3) waiver is also for Dr. Hennekens' membership on two data safety monitoring boards for a competitor of Crestor. He receives less than $10,001 per year for membership on a competitor's advisory board where he receives less than $10,001 per year and for membership on a competitor's data safety monitoring board. He receives less than $10,000 per year.

Finally, the waiver includes consulting for two of Crestor's competitors. He receives less than $10,001 per year from each firm.

Dr. Jeffrey Kopp has been granted a waiver under 18 U.S.C. 208(b)(3) for his consulting for a competitor on unrelated matters. The less than $10,001 per year is donated to charity.

Dr. Nelson Watts has been granted a waiver under 18 U.S.C. 208(b)(3) for his consulting for two competing firms on unrelated matters. He receives between $10,001 to $50,000 per year from each firm.

Dr. Margaret Wierman has been granted a

waiver under 18 U.S.C. 208(b)(3) for her membership on a competitor's speakers bureau. She receives between $10,001 to $50,000 a year annually, also for her membership on another competitor's speakers bureau. Less than $5,000 is paid directly to Dr. Wierman's employer for her research accounts.

Dr. Paul Woolf has been granted waivers under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Act for ownership of stock in one of Crestor's competitors valued between $25,001 and $50,000.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, we would like to disclose that Dr. John Neylan is participating in this meeting as an acting industry representative acting on behalf of regulated industry. In the event that the discussions involved any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their

exclusion will be noted for the record.

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

DR. BRAUNSTEIN: Thank you.

Dr. Kopp, perhaps you will tell the audience who you are and what you do.

DR. KOPP: My name is Jeffrey Kopp. I am a nephrologist with the NIDDK Intramural Research Program.

DR. BRAUNSTEIN: Thank you.

Dr. Catherine McComus has a brief announcement.

Announcement

DR. McCOMUS: Good morning. My name is Catherine McComus. I am a faculty member at the University of Maryland. I am here today to ask for your help on a study that I am conducting with the FDA on what the public knows and understands about the conflict-of-interest procedures that the FDA uses to monitor and manage real or potential conflicts of interest of its advisory-committee members.

This is a study that is being conducted

across multiple centers at the FDA. This, I believe, is the tenth meeting where I have collected data. I have distributed questionnaires for members in the audience. I have also distributed a separate questionnaire for the advisory-committee members. If you have a chance to complete it today, there is a box outside this room where you can deposit it. Otherwise, there is a business-reply envelope that you can drop it in and mail it back at your convenience.

I do hope that you will take a few moments to complete this survey. They are anonymous and the more responses we get, that better we are able to represent how people feel about the conflict-of-interest procedures and to provide recommendations to the FDA on how we might improve satisfaction with the procedures.

I will be around today if you have any questions. There is also my contact information and a letter that is in the survey research and please feel free to contact me if you have any questions.

Thank you very much for allowing me to address the group.

DR. BRAUNSTEIN: Thank you.

Dr. David Orloff will give his introductory comments.

Welcome and Introductory Comments

DR. ORLOFF: Good morning. First, I want to thank the members of the committee and the invited consultants for their review of the materials beforehand, obviously, and for their agreement to participate in today's meeting.

I don't know if Dr. Braunstein noted it, but Dr. Kreisberg, Robert Kreisberg, who was supposed to be attending today as a consultant for the FDA, was unable to attend due to a last-minute conflict.

I also want to thank the FDA reviewers, primarily Dr. William Lubas and Joy Mele, for their work not only in reviewing the NDA but in preparing for today's meeting.

I have some brief introductory remarks that I will just read, if that is okay with everyone. Crestor is the seventh HMG CoA-reductase inhibitor, or statin, to come before the FDA for review of data addressing safety and efficacy going back to lovastatin, approved in 1987. Since the approval of lovastatin, as most in the room understand, much has been learned about the risks

and benefits of this class of drugs and of individual members, some, perhaps, more than others.

With regard to efficacy, HMG CoA-reductase inhibition, as a pharmacologic approach to lipid altering, favorably impacts the course of atherosclerotic cardiovascular disease in a broad range of populations across ages, genders, concomitant risk factors, those with diabetes or without diabetes, in patients with high or low LDL cholesterol and in those with normal or low HDL cholesterol.

The controlled clinical-trials experience with this class includes nearly 30,000 statin-treated patients followed in five-year placebo-controlled trials examining hard cardiovascular outcomes as well as noncardiovascular serious morbidity and mortality.

Suffice it to say that lowering LDL cholesterol with HMG CoA-reductase inhibitors in at-risk individuals is, I think, irrefutably proven to reduce all the manifestations of atherosclerotic cardiovascular disease including cardiovascular mortality with no evidence from those trials of a countervailing excess of noncardiovascular deaths.

This, then, is a remarkably effective class of drugs.

With regard to specific aspects of the safety profile of the statins, it has long been known that statin use is associated with a dose-related increase incidence of mild to moderate asymptomatic, often transient and resolving on therapy, elevations in hepatic transaminases. Rare cases of serious liver injury have been reported in association with statin use although causality has been difficult to establish. I would say that, by and large, these drugs are safe with regard to the liver.

Also long known, although not well understood, is a potentially much more serious side effect of statins, myopathy. This adverse effect presents across a broad clinical spectrum from asymptomatic creatine-kinase elevations to marked creatine-kinase elevations with symptoms to full-blown rhabdomyolysis.

From clinical trials, we know that marked creatine-kinase elevations with or without clinically evident myopathy, which we consider surrogates for rhabdomyolysis risk, occur with increasing frequency at increasing doses of drug.

The risk of myopathy in rhabdo appears further related to a number of different factors, some better understood than others; for example, systemic bioavailability of drug, pharmacokinetic interactions leading to augmented drug exposure, the "affinity," in quotes, if you will, of drug for muscle, the potency of the drug as an inhibitor of HMG CoA-reductase and predisposing factors such as diabetes, renal failure, hypothyroidism, surgery, severe acute illness or injury.

Rhabdomyolysis, or fulminant myopathy with frank necrosis, myoglobinemia and myoglobinuria and acute pigment-induced renal failure occurs very rarely in the clinic in, at least retrospectively, uniquely susceptible individuals in whom it appears, after the fact, that some threshold muscle exposure to drug has been exceeded. As above, as I stated earlier, this is the most serious side effect of statins, potentially fatal, and the dose-limiting toxicity.

Finally, in the Crestor Development Program, a heretofore undescribed renal side effect of an HMG CoA-reductase inhibitor has been observed.

The original New Drug Application for

Crestor was submitted on June 26, 2001. An approvable action was taken by the agency on May 31, 2002, based on safety concerns arising out of the initial review regarding muscle and kidney. More specifically, several cases of severe myopathy or rhabdomyolysis occurred in patients treated with 80 milligrams daily, the highest dose initially proposed.

There were no cases seen at 40 milligrams, although patient exposures at 40 milligrams were far fewer. Based on this primary safety concern and the marginal incremental LDL lowering seen with the step from 40 to 80 milligrams, the agency concluded that 80 milligrams should not be approved.

Because the clinical-trial exposures had been skewed toward the low and high ends of the proposed dosage range, further data were deemed necessary before a decision could be reached on the 20 and 40 milligram doses. The FDA requested that the sponsor conduct additional trials to augment the patient exposure at 40 milligrams specifically as 40 milligram starts, patients de novo treated with Crestor at a dose of 40 milligrams, in order to answer this important question, is Crestor more

prone to cause myopathy than currently marketed statins, or, alternatively, was 80 milligrams simply too high a dose to be, overall, safe for use.

This question was particularly important in light of the experience with Baycol, cerivastatin, which, as was observed post-approval, conferred substantial risk of myopathy relative to other members of the class, a doses effecting little LDL-cholesterol lowering.

In response to the FDA request, the sponsor has studied the myopathic risk associated with Crestor use in a very large premarketing patient exposure, indeed, by far the largest of any statin brought before the FDA. The sponsor and the FDA medical officer, Dr. Lubas, will present data today that suggests that the risk of myopathy with Crestor relative to LDL-lowering efficacy is, at the very least, no greater than that with the other marketed members of the class. I emphasize the critical importance of this issue in the evaluation of the safety of this drug.

In addition, the sponsor was asked to investigate further the finding of new-onset mild proteinuria observed mostly in patients taking

Crestor 80 milligrams. Specifically, the sponsor was charged with investigating the "nature, magnitude and frequency" of renal adverse events observed in patients treated with rosuvastatin and to explore whether these effects were "reversible, chronic or progressive."

As you will hear presented, the renal effects occur with very low frequency at doses below 80 milligrams although in up to 10 percent of patients taking 80 milligrams. This is not a finding noted in other statin-development programs or in long-term trials of statins.

The clinical picture of Crestor-associated renal effects seems to include variably the combination of low-grade proteinuria, minor elevations in creatinine and microscopic hematuria. This will be discussed by Dr. Lubas and by the sponsor.

The sponsor, furthermore, will present information supporting the possibility that these renal effects represent a mechanism of action-related class effect of statins on the proximal statins on the proximal renal tubule. This requires close attention and discussion in the evaluation of the safety of this drug.

In addition, the FDA clinical and statistical reviewers will make further comments on specific efficacy and safety issues.

I will end my comments there and have a few more remarks at the time that I charge the committee later during the proceedings. Thank you very much.

DR. BRAUNSTEIN: Thank you Dr. Orloff.

We will now move on to the sponsor's presentation.

NDA 21-366 Crestor (rosuvastatin calcium) tablets

AstraZeneca Pharmaceuticals

Agent for iPR Pharmaceuticals Incidence.

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Sponsor Presentation

Introductory and Regulatory Overview

MR. ELIASON: Good morning everyone. My name is Mark Eliason and I am the US Regulatory Director for CRESTOR at AstraZeneca.

[Slide.]

Mr. Chairman, distinguished members of this committee, AstraZeneca is pleased to present information regarding the safety and efficacy of CRESTOR Tablets, as currently contained in our NDA. We hope that you will find our presentations this

morning to be helpful in your deliberations later in the day.

On behalf of AstraZeneca, I wish acknowledge at this time the multitude of physicians, and other healthcare professionals who participated in the very large CRESTOR drug development program.

To begin my presentation, I d like to discuss the development objectives established by AstraZeneca for a new statin candidate.

[Slide.]

From the early information derived from the molecule, we focused on the development of rosuvastatin to provide an overall benefit risk profile demonstrating:
greater beneficial effects on key lipid parameters, at both the start dose and across the dose range, when compared to approved drugs in this class; a similar safety profile in relation to muscle, liver, and other effects, when compared to approved drugs in the statin class; and, lastly, a low potential for significant drug-drug interactions, especially through the Cytochrome P450 and P-glycoprotein systems, as plasma levels of other drugs in this class had been shown to be driven

higher due to drug-drug interactions.

[Slide.]

Rosuvastatin is a novel synthetic inhibitor of HMG-CoA reductase that was discovered by the Shionogi Company of Japan. In terms of its structure, at first glance rosuvastatin is a conventional statin as it resembles other statins in having the common pharmacophore group, the group that resembles the HMG substrate.

However, rosuvastatin is distinctive in its structure as it contains a relatively polar methane sulfonamide group. This helps to place rosuvastatin low on the scale of lipophilicity, near pravastatin, when plotted against the other statins as shown on the scale on the right of this slide.

This has two consequences for pharmacology: first, compounds with low lipophilicity have the potential of being highly selective for entry into liver cells as compared to non-hepatic cells. Secondly, compounds low on this scale are relatively water soluble and therefore would not require extensive metabolism by the hepatic CYP P450 system to render them sufficiently water soluble for excretion.

In essence, preclinically, rosuvastatin has some of the favorable properties of pravastatin, namely a high degree of cell selectivity and a low degree of metabolism by the cytochrome P450 system.

[Slide.]

On this slide, I would now like to briefly summarize the key pharmacokinetics and disposition characteristics of rosuvastatin. The absolute bioavailability of rosuvastatin is approximately 20 percent. The molecule is only moderately bound to plasma proteins, principally albumin.

Rosuvastatin does not undergo extensive metabolism in man. Finally, the terminal half-life of rosuvastatin is approximately 16 to 20 hours.

[Slide.]

Moving to our clinical program, our NDA is supported by a large international clinical development program. The results of the studies outlined on this slide will be discussed later in our presentations. The program included thirty-three Phase I studies, and twenty-seven Phase II/III trials. During Phase III, we evaluated doses from 5 to 80 milligrams.

The safety database from this set of Phase

II/III trials now contains over 12,500 patients taking rosuvastatin having a total of over 14,000 patient years. As Dr. Orloff had stated earlier today, this is by far the largest initial approval NDA database submitted for a statin to date.

The design of the Phase III program trials included comparative trials to both placebo and key statin therapies, which included atorvastatin, simvastatin and pravastatin, as well as to non-statin therapies, such as niacin and fenofibrate in hypertriglyceridemic patients. In addition, we studied rosuvastatin in combination with niacin and with fenofibrate, as well as cholestyramine.

At the completion of the controlled portion of our Phase III trials, the enrolled patients were allowed to continue into long-term rosuvastatin open-labeled extension trials. These open label extensions are all still active and continue to add valuable long-term rosuvastatin safety information to the clinical database.

[Slide.]

There were a number of important trial features in the clinical development program for rosuvastatin, some of which are presented here on

this slide. For our Phase III program, all clinical laboratory samples were analyzed at one central laboratory. This reduced the potential for inter-lab variability.

As you will see later in our presentations, we also tried to be as inclusive as possible in the range of patients enrolled in our Phase II/III trials. The purpose of this was to recruit a diverse population of patients, in various states of health, that would be considered representative of the general population requiring statin therapy.

To be specific, we had no upper age limit for our trials so that approximately a third of the patients participating in our trials were over 65 years of age.

For most of our trials, we allowed patients with creatinines of up to two and a half milligrams per deciliter. From this, over 50 percent of the patients enrolled in our trials had some degree of renal insufficiency.

Women of childbearing potential were permitted to enter into most trials, provided that they were not pregnant and used appropriate contraception. Finally, we allowed patients into

trials with existing co-morbidities, such as hypertension, diabetes, and cardiovascular disease, provided that the patient's condition was stable prior to randomization.

[Slide.]

Now I would like to turn to the Crestor NDA itself. As Dr. Orloff had previous stated, our original new drug application for CRESTOR Tablets was submitted to the FDA in June of 2001. The initial NDA submission proposed a dose range of 10 to 80 milligrams once daily for rosuvastatin.

As further clinical data became available, it was evident that the 80-milligram dose provided additional lipid effects that would be of potential benefit to those patients with difficult-to-control dyslipidemias.

However, the emergent profile for the 80-milligram dose did not meet our objectives for the favorable benefit-risk profile for the general populations. So, in March of 2002, AstraZeneca and the Review Division agreed to suspend further development of the rosuvastatin 80-milligram dose for the general population, and all patients who were receiving the 80-milligram daily dose had their dose reduced to 40-milligram daily.

[Slide.]

The NDA action letter was issued in May 2002, noting that the proposed 10, 20 and 40 -milligram doses of rosuvastatin were approvable. The NDA action letter centered on the request for additional safety data for patients receiving the 20 and 40-milligram, in order to fully assess the therapeutic index of rosuvastatin. In addition, the Division requested additional information regarding the renal effects observed in the program.

AstraZeneca and Division representatives met in July 2002 to outline the data package for responding to the action letter. At this meeting, the Review Division requested that a minimum of 600 patients treated with rosuvastatin at the 20 milligram and at the 40-milligram for six months be included in the response.

From that, an NDA amendment was submitted in February of this year supporting a proposed 10 to 40-milligram dose range for the general population. The NDA amendment provided the requested additional safety information for the 20 and 40-milligram doses, and with the submission of an interim safety update in June of this year, the

final NDA safety database contains over 12,500 patients treated with rosuvastatin.

[Slide.]

The Rosuvastatin Clinical Development Program supports the proposed CRESTOR Tablet NDA indications which are fully presented in Section 1.1 of our briefing document. I will, just for time's sake, go through them here very quickly.

Our first indication involves primary hypercholesterolemia and mixed dyslipidemia. A second indication involves patients with hypertriglyceridemia. Finally, a third indication involves the genetic familial homozygous hypercholesterolemic patient population.

[Slide.]

The dosing recommendations proposed in the CRESTOR NDA are outlined on this slide. For primary hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia, the recommended start dose of CRESTOR is 10 milligrams, once daily, with a maximum recommended daily dose of 40 milligrams.

A 20-milligram start dose is optional for patients with LDL-C levels of greater than 190 milligrams per deciliter and aggressive lipid targets. For the homozygous familial

hypercholesterolemia indication, the recommended starting dose for CRESTOR is 20 milligrams once daily.

Finally, a 5-milligram dose will be made available for patients taking cyclosporine.

The rationale regarding these dosing recommendations will be discussed in our presentations

[Slide.]

Regarding the status of the CRESTOR, we have approval in 24 countries in Europe, Asia and the Americas, all incorporating the 10-milligram to 40-milligram dose range. In addition to the described NDA activity, we continue to study rosuvastatin. Our ongoing trials program, investigating rosuvastatin in cardiovascular risk reduction, currently includes approximately 24,000 patients in the U.S. and the rest of the world all who are taking rosuvastatin.

Also, as part of this program, we have initiated two clinical-outcomes trials in May of this year, which will enroll a total of 18,000 patients between them.

[Slide.]

With this background in mind, here is the

agenda for remainder of our presentation. Next, Dr. James Blasetto will present a brief overview of the key efficacy results from our NDA clinical development program.

After Dr. Blasetto, Dr. Howard Hutchinson will discuss the safety profile of rosuvastatin from our NDA clinical program, with a focus on key safety issues from the statin drug class.

Finally, AstraZeneca has invited Dr. Daniel Rader, from the University of Pennsylvania, to present his thoughts as a practicing physician on the potential role of rosuvastatin in treating hypercholesterolemia.

[Slide.]

AstraZeneca has also asked the following individuals to assist in responding to any points that the advisory committee members may wish to have addressed during this meeting. In addition to Dr. Rader, we have Dr. Christie Ballantyne from Baylor College, Dr. Donald Hunninghake from the University of Minnesota, Dr. Edmund J. Lewis from Rush Presbyterian St. Luke's Medical Center, Dr. Thomas Pearson from the University of Rochester Medical Center and Dr. Evan Stein from Medical Research Laboratories International.

Now I would like to introduce Dr. James Blasetto, Senior Director at AstraZeneca, who will present the efficacy portion of our presentation.

Dr. Blasetto?

Clinical Development

Efficacy Overview

DR. BLASETTO: Good morning.

[Slide.]

I am Dr. James Blasetto, Senior Director, Clinical Research at AstraZeneca.

[Slide.]

Hypercholesterolemia represents a significant, persistent yet potentially treatable medical program in the United States. If we look at the evolution of the Cholesterol Management Guidelines as proposed by the National Cholesterol Education Program, we see an ever-increasing need for more lipid-modifying efficacy.

If we focus in on the most recent guidelines, the ATP-3 Guidelines launched in 2001, we see a number of new and important features. Firstly, identifies the optimal LDL-C level at less than 100 milligrams per deciliter.

Secondly, the target goal for patients in the high-risk group has been made more aggressive,

less than 100 milligrams per deciliter, and a number of patients that qualify for the high-risk group has been expanded with the introduction of the CHD risk-equivalent patients.

Thirdly, there is an increased focus on HDL-C with a secondary target for therapy, the non-HDL-C goal, for patients with persistent elevated triglycerides. Thus, with the current guidelines, it is estimated that over 36 million patients will require lipid-lowering therapy and approximately 60 percent of those, or approximately 21 million, will require a treatment LDL-C goal of less than 100 milligrams per deciliter.

[Slide.]

Yet, if we look at recent clinical data, we see that a treatment gap still exists between what current therapies can obtain and what is needed. This is data that was presented by Dr. Christie Ballantyne in 2001 from the ACCESS Trial, the Atorvastatin Comparative Cholesterol Efficacy and Safety Study.

This is a cohort of patients in the CHD risk category. Patients were treated and titrated up to achievement of the ATP-2 goal, an LDL-C of less than or equal to 100 milligrams per deciliter.

If we focus in on the patients that were treated with up to maximum doses of atorvastatin, 80 milligrams, we see that 28 percent of the patients did not achieve their LDL-C target goal and approximately 40 percent of the patients did not achieve an established non-HDL-C goal.

If we look at the percent of patients that did not achieve their LDL or non-HDL-C goals with the other statins at the doses studied, we see the numbers were even greater. Thus, with the current guidelines, more patients require more aggressive treatments yet, with current therapies, a treatment deficit still exists.

[Slide.]

Now, as you heard in the opening remarks, there were three key objectives that were core to our Clinical Development Program. My presentation will focus on efficacy data to support the first key objective which was to demonstrate greater beneficial effects on key lipid parameters over currently marketed statins. In addition, I will discuss data that addresses efficacy questions raised to this advisory committee.

[Slide.]

Our first LDL efficacy data came from two

Phase II dose-ranging studies. These studies were prospectively designed to be pooled. The patient population evaluated were patients with Type IIa and IIb hypercholesterolemia.

This is the response seen in percent change from baseline in LDL-C at each of the doses evaluated. The mean age in the population studied was 56 years and the mean baseline LDL-C, 190 milligrams per deciliter. Statistically significant differences compared to placebo at each of the doses evaluated were seen, a 33 percent reduction up to a 65 percent reduction in LDL-C.

Now, based on the efficacy that we saw in these dose-ranging studies, we initially chose to evaluate two potential starting doses, rosuvastatin 5 milligrams and rosuvastatin 10 milligrams.

[Slide.]

Our Phase III data has confirmed the added benefits on key lipid parameters with the 10-milligram dose compared to the 5-milligram dose with an indistinguishable safety profile.

This is data from five clinical trials in our Phase III program which was prospectively designed to be pooled. The patient populations studied were patients with Type IIa and IIb

hypercholesterolemia. The mean age in the population was 58 with a mean baseline LDL-C of 187 milligrams per deciliter.

After twelve weeks of treatment, this is the response seen in key lipid parameters with rosuvastatin 10-milligrams and rosuvastatin 5 milligrams. The 10-milligram dose added benefit on all lipid parameters compared to the 5-milligram dose, in particular, a 6 percent further LDL-C reduction and an approximate 5 percent further non-HDL-C reduction.

Thus, the risk-benefit profile of the 10-milligram dose is better than the 5-milligram dose and offers a better treatment option as a starting dose for patients. Thus, our proposed starting dose for the general population is rosuvastatin 10 milligrams.

Alternatively, we initially evaluated doses up to and including the 80-milligram dose. As you heard in the opening remarks, after an assessment of the benefit-risk profile of the 80-milligram dose, we elected to back-titrate patients from 80 milligrams to 40 milligrams and not to pursue at this time further development of the 80-milligram dose. Thus, the maximum proposed

dose is rosuvastatin 40 milligrams.

Rosuvastatin 40 milligrams offers benefit in key lipid parameters compared to the 20-milligram dose for patients requiring more reductions to achieve their NCEP targets.

[Slide.]

This is data from five individual clinical trials in our development program which looks at the effects on LDL-C with rosuvastatin 40 milligrams and rosuvastatin 20 milligrams. In each of these trials, the patient populations studies were patients with Type IIa and IIb hypercholesterolemia with a cohort of patients with heterozygous familiar hypercholesterolemia evaluated in Trial 30.

In each of these clinical trials, the 40-milligram dose added greater reductions in LDL-C compared to the 20-milligram dose. In four or five of the clinical trials, there was a 7 percent or greater LDL-C reduction seen with the 40-milligram dose compared to the 20-milligram dose. Thus, for patients requiring more reductions in LDL-C or non-HDL-C to achieve their NCEP target goals, the 40-milligram dose offers benefits over the 20-milligram dose.

Thus our proposed dose range is rosuvastatin 10 to 40 milligrams and, for the remainder of my presentation, I will focus on the 10 to 40-milligram dose range.

[Slide.]

We studied the effects comparatively of rosuvastatin in several clinical trials.

[Slide.]

The largest clinical trial comparatively done was the STELLAR Trial, Trial 65, as presented here. This trial included over 2,000 patients. After a six-week dietary lead-in, patients were randomized in an open-label fashion to one of the treatment arms with rosuvastatin, atorvastatin, simvastatin or pravastatin, as shown, for six weeks of treatment.

Baseline characteristics in all treatment arms were well-matched. The mean age in the population was 57 and the mean baseline LDL-C 189 milligrams per deciliter.

[Slide.]

After six weeks of treatment, this is the response seen in percent change from baseline in LDL-C. Rosuvastatin, 10 to 40 milligrams on a milligram-to-milligram basis demonstrated greater

reductions than atorvastatin, simvastatin and pravastatin.

Doubling of the dose of statin therapy yielded an approximate 4.5 to 5 percent further LDL-C reduction. If we assess the effects of patients treated with rosuvastatin 40 milligrams to those treated with atorvastatin 80 milligrams, we saw an approximate 4 percent further LDL-C reduction with rosuvastatin therapy.

[Slide.]

If we look at the distribution of LDL-C at each of the treatment arms, we see that the distribution of LDL-C was similar in each treatment arm, the number of outliers was similar and the median reduction in LDL-C seen with rosuvastatin 40 milligrams was greater than that seen with the other statin comparators.

[Slide.]

The STELLAR Trial was designed to perform multiple pairwise and dose-to-dose comparisons on other key lipid parameters. This is the response in HDL-C after six weeks of treatment in each of the treatment arms evaluated. Rosuvastatin 20 and 40 milligrams raised the HDL-C approximately 10 percent.

Comparatively, the 10-milligram-response rosuvastatin was statistically greater than the 10-milligram response of pravastatin. The 20-milligram-response rosuvastatin was statistically greater than the 20 to 80-milligram response of atorvastatin, the 20 and 40-milligram response of pravastatin and the 40-milligram response of simvastatin. The 40-milligram response of rosuvastatin was greater than the 40 and 80-milligram response of atorvastatin and the 40-milligram response of both simvastatin and pravastatin.

[Slide.]

We assessed the results on the important parameter non-HDL-C goal. Rosuvastatin, at the 40-milligram dose, reduced non-HDL-C by greater than 50 percent. Comparatively, compared to similar doses of atorvastatin and similar doses, or higher doses, of simvastatin and pravastatin, rosuvastatin reduced non-HDL-C by a greater percent.

[Slide.]

Now, to assess the effects on achievement on NCEP targets at higher doses, we evaluated rosuvastatin comparative to atorvastatin in a

titration-to-goal study, Study 26.

[Slide.]

This is the design of that trial. After a six-week dietary lead-in, patients were randomized in a double-blind fashion to one of the treatment arms with rosuvastatin or a common starting dose, atorvastatin 10 milligrams, for twelve weeks of active treatment.

After twelve weeks, patients were then subsequently titrated to the next highest dose if they did not achieve their ATP-2 LDL-C targets. Baseline characteristics in each of the treatment arms were well matched. In this population of patients with Type IIa and IIb hypercholesterolemia, the mean age was 57 and the mean baseline LDL-C 187 milligrams per deciliter.

[Slide.]

After 52 weeks of treatment, this is the response seen in the percent of patients achieving target goal. 82 percent of the patients on rosuvastatin 10 milligrams achieved their target goal without need for titration compared to 59 percent of the patients on atorvastatin 10 milligrams.

Overall, 96 percent of the patients

achieved target goal with a regimen of rosuvastatin 10 to 40 milligrams compared to 87 percent of the patients with a regimen of atorvastatin 10 to 80 milligrams. Thus, overall, more patients achieved their target goal but, in particular, a greater percentage achieved target goal at the starting dose without need for titration.

[Slide.]

I would like to conclude with an assessment of rosuvastatin in an important population of patients, patients with severe hypercholesterolemia, heterozygous familial hypercholesterolemia. This represents an important population of patients because of the severe nature of their hypercholesterolemia. They are difficult to treat and have a frequency in the United States population of approximately 1 in 500.

[Slide.]

We assessed the effects of rosuvastatin comparatively in this population in Trial 30. This is the design of that trial. It was a large, multicentered, multinational trial. After a six-week dietary lead-in, patients were randomized in a double-blind fashion to rosuvastatin or atorvastatin 10 milligrams.

In view of the severe hypercholesterolemia at baseline these patients had, and the increased efficacy they needed at the start of therapy, we chose a strategy of starting these patients to evaluate a 20-milligram starting dose. After six weeks of treatment, the patients were force-titrated to the 40-milligram dose and then ultimately to the 80-milligram dose.

Baseline characteristics were well matched in both treatment arms. The mean age of the population was 48, somewhat younger than the data I previously presented. That is not unexpected with patients with heterozygous familial hypercholesterolemia. The baseline LDL-C demonstrates the severe hypercholesterolemia of these patients approaching nearly 300 milligrams per deciliter.

The results of the 80-milligram dose will be presented to show the potential added benefits of increased efficacy. However, in view of our proposed dosing recommendations, I will focus my comments on the 20 and 40-milligram dose response for rosuvastatin.

[Slide.]

This is the response in the percent change

from baseline in LDL-C at each of the time points and doses evaluated. Rosuvastatin 20 milligrams reduced LDL-C 47 percent and 54 percent reduction at the 40-milligram dose, statistically greater than the 20 and 40-milligram dose response seen with atorvastatin.

[Slide.]

If we evaluate the effects on HDL-C, a 12 percent and 10 percent increase in HDL-C seen with 20 and 40 milligrams of rosuvastatin, statistically greater than the 20 and 40-milligram response seen with atorvastatin.

[Slide.]

The greater LDL-C reduction translated into more patients achieving their ATP-3 target goals. 37 percent of the patients with rosuvastatin 20 milligrams achieved the target goal and nearly 50 percent with rosuvastatin 40 milligrams, both statistically greater than the 20 and 40-milligram response of atorvastatin.

[Slide.]

If we focus in on that high-risk group of patients requiring a target LDL-C of less than 100 milligrams per deciliter, 17 percent of the patients achieved that target goal with

rosuvastatin 40 milligrams compared to 3 percent of the patients with atorvastatin 40 milligrams. This was statistically different.

[Slide.]

So, in summary, data from our Clinical Development Program has demonstrated rosuvastatin 10 to 40 milligrams reduced LDL-C 50 to 62 percent as presented in the dose-ranging studies. Rosuvastatin lowered LDL-C and non-HDL-C more than atorvastatin, simvastatin and pravastatin across the dose range. Greater increases in HDL-C were observed.

More patients achieved NCEP goals with a regimen of rosuvastatin 10 to 40 milligrams than that with atorvastatin 10 to 80 milligrams, simvastatin 20 to 80 milligrams and pravastatin 20 to 40 milligrams.

I thank you and, at this time, I would like to introduce Dr. Howard Hutchinson who will discuss the safety profile of rosuvastatin.

Clinical Development

Safety Review

DR. HUTCHINSON: Good Morning.

[Slide.]

I am Howard Hutchinson, Vice President for Clinical Research at AstraZeneca. Today, I am

pleased to be here to present the safety profile for rosuvastatin.

[Slide.]

Dr. Blasetto presented the efficacy data showing the overall benefits of a rosuvastatin 10-milligram to 40-milligram dose range for the treatment of patients with dyslipidemia. However, the benefits of a new drug must also be placed in the context of the potential risks associated with its use.

With this in mind, I will now present data which addresses the last two objectives of our development program. This information will show that the proposed 10-milligram to 40-milligram dose range for rosuvastatin has a safety profile similar to other marketed statins, and that rosuvastatin will have a low potential for significant drug-drug interactions.

[Slide.]

The safety data I am going to present today comes from twenty-seven clinical trials conducted worldwide.
About half the patients were from the United States.
The overall database is comprised of over 12,500

patients who have had over 14,000 patient years of treatment with rosuvastatin at doses up to and including 80 milligrams.

[Slide.]

In presenting the safety data, I will focus on several key areas. First, I will present the overall demography of our patient population followed by exposure data, and adverse events. I will then focus on three areas of interest for rosuvastatin and statins in general. They are the liver, skeletal muscle, and renal effects. I will finish with a brief presentation on drug-drug interactions.

[Slide.]

This slide represents the overall demography for patients in our all-controlled/uncontrolled plus Real Time Laboratory Data or RTLD Pool. This pool represents our largest pool with 12,569 patients and includes patients exposed to rosuvastatin in both controlled trials and in open-label extension trials.

As shown, the mean age for subjects in our program was 58. Approximately one-third of the patients were 65 years or older, and over 900 were 75 or over. Almost half of the population was

female, and two-thirds of the women were post-menopausal.

[Slide.]

With regard to ethnicity, most patients were Caucasian; however, over 1000 patients were of non-Caucasian descent.

[Slide.]

We set up our development program to be inclusive. Patients with co-morbid conditions were permitted to enter studies provided they were stable at baseline and we allowed patients to enter most trials with a serum creatinine level up to 2.5 milligrams per deciliter.

As shown, over half of the subjects enrolled in the program had baseline renal impairment as determined using the Cockroft-Gault formula. In addition, over half of the subjects had baseline hypertension, 36 percent had documented atherosclerotic cardiovascular disease, and 16.5 percent had diabetes.

[Slide.]

This slide shows the maximum continuous duration of treatment with the 5-milligram to 80-milligram doses of rosuvastatin from the clinical trial program. As shown, over 1000

patients were treated with each of these doses. Importantly, over 7800 patients were treated with 10-milligram proposed starting dose, over 3900 patients were treated with the 20-milligram dose, and over 4000 were treated with the 40-milligram dose. Of the 4000 subjects treated with the 40-milligram dose, over 2000 initiated therapy at this dose.

Highlighted are the 24-week and 48-week exposures. Note that over 1300 and 1800 patients were treated with the 20-milligram and 40-milligram doses for 24 weeks or longer. 545 and 276 were treated with these doses for greater than or equal to 48 weeks. As previously discussed, patients on 80 milligrams were back-titrated to 40 milligrams during the development program. The 40-milligram exposures seen in this table represent patients back-titrated from 80 milligrams and patients never exposed to 80 milligrams. Importantly, however, all of the exposures greater than 48 weeks are in patients who were never exposed to the 80-milligram dose and over 3700 patients in this pool were never exposed to the 80-milligram dose.

The last column is the greater than or equal to 40-milligram treatment group. In this

group, patients treated with 80-milligram dose and back-titrated to 40 milligrams were considered to have been treated continuously with rosuvastatin with at least 40 milligrams of drug.

This group is important because it gives information regarding the potential for adverse events to occur very late into therapy. Note that 1165 patients were treated for greater than or equal to 48 weeks in this group and 874 for greater than or equal to 96 weeks in this group.

As you will see, the exposures generated for this analysis are appropriate for evaluating the overall safety of rosuvastatin at doses up to and including 80 milligrams.

[Slide.]

Today, a detailed review of patient-reported adverse events will not be presented so that I can focus on the more critical issues addressed in the FDA briefing document. Shown here are the key points summarizing the adverse event data.

First of all, the data showed that the frequency and types of adverse events reported for rosuvastatin were similar to that of the comparator statins in our program. Second, the frequency and

types of adverse events were similar for the 5-milligram, 10-milligram, 20-milligram and 40-milligram doses of rosuvastatin.

However, at the 80-milligram dose, increased frequencies of nausea, myalgia, asthenia, and constipation were observed, in particular, nausea, myalgia, asthenia and constipation. Importantly, rosuvastatin was well-tolerated in a broad spectrum of patients regardless of age, sex, ethnicity, the presence comorbidities such as diabetes, hypertension, or renal impairment, and in patients on medications used to treat comorbid conditions such as anti-hypertensive agents and anti-diabetic agents.

[Slide.]

I would now like to turn our attention to the effects of rosuvastatin on three organs, the liver, skeletal muscle, and kidneys. I will start with the liver.

As Dr. Orloff had mentioned earlier, in general, statins are well tolerated from the perspective of the liver. Asymptomatic transaminase elevations are reported for all statins, and the frequency of the elevations appears to increase with dose. Importantly, these

elevations have almost never been associated with liver failure. The effects of rosuvastatin on the liver are similar to that observed with other members of the class.

[Slide.]

In the rosuvastatin program, liver function tests were performed at each visit. In this section, I will present the percentage of patients with ALT elevations greater than three times the upper limit of normal on two occasions. Note that the ALT elevations greater than three times the upper limit of normal on two occasions is consistent with the definition of persistent elevations used in the labels for other marketed statins.

I will not present data on AST elevations. However, AST elevations in our program mirrored the ALT elevations.

We also evaluated patients for ALT elevations associated with increases in bilirubin. Importantly, these elevations were rarely observed, and, in those instances where they were observed, they were almost always associated with another illness such as a malignancy or infectious hepatitis.

[Slide.]

Shown on this slide is the frequency of persistent ALT elevations in patients treated with rosuvastatin from 5 to 80 milligrams in the all Controlled/uncontrolled plus RTLD Pool. The data shows that the frequency of persistent ALT elevations ranged from 0.1 percent to 0.5 percent at rosuvastatin doses from 5 to 40 but increased to 1.4 percent at the 80-milligram dose.

[Slide.]

This figure helps to put the overall ALT results from the rosuvastatin program into context with that reported in the prescribing information or summary basis of approval documents for other marketed statins, specifically fluvastatin, 20, 40, and 80 milligrams, lovastatin, 20, 40, and 80 milligrams, simvastatin, 40 and 80 milligrams, atorvastatin, 10, 20, 40, and 80 milligrams and the data for rosuvastatin.

On the x-axis is plotted the percentage LDL-C lowering for the various doses of drug which represents the potential benefits that can be achieved at a particular dose. On the y-axis, the frequency of persistent ALT elevations at a given dose represents a potential risk of the dose. Note

that rosuvastatin at doses from 5 to 40 milligrams has a low frequency of elevations similar that observed with other statins. Only at the 80-milligram dose is an increase in frequency of persistent elevations seen. The increase in frequency with rosuvastatin at the 80-milligram dose, however, is in the range observed for marketed statins. However, the increase observed with the other marketed statins occurs at lower levels of LDL-C reduction.

Overall, the data pertaining to possible liver effects of rosuvastatin obtained from our development program support its safety with regard to this organ.

[Slide.]

I would now like to turn our attention to skeletal-muscle findings. Similar to persistent ALT elevations, adverse skeletal-muscle effects are a recognized complication of statin therapy. Adverse effects such as myopathy and rhabdomyolysis have been reported for all statins. However, the frequency of such reports is very low within the recommended dose range.

[Slide.]

Similar to the routine evaluation of

liver-function tests in our program, creatine kinase or CK measurements were performed at each visit also.

In this part of my talk, I will present the following information.

First, I will present data on CK elevations greater than ten times the upper limit of normal. This is an objective measure of the potential of a statin to cause muscle effects.

Next, I will present our cases of myopathy. In our program, we used a well established definition of myopathy which is CK elevations greater than ten times the upper limit of normal with associated muscle symptoms. Some of the patients in our program had rhabdomyolysis at the 80-milligram dose.

Currently, rhabdomyolysis is defined several different ways in the literature. In the FDA review, rhabdomyolysis cases are defined as those patients with myopathy who required hospitalization to receive intravenous fluids.

[Slide.]

Shown on this slide is the frequency of both symptomatic and asymptomatic CK elevations in patients treated with rosuvastatin at doses from 5

to 80 milligrams, once again in our largest pool, the all controlled/uncontrolled plus RTLD Pool. Our data shows that the frequency of elevations ranged from 0.2 to 0.4 percent at rosuvastatin doses from 5 to 40 but increased to 1.9 percent at the 80-milligram dose.

If we now look at these cases for patients with muscle-related symptoms, we have our overall myopathy group.

[Slide.]

Shown on this slide are all symptomatic CK elevations and those with a possible relationship to treatment. Note that the overall number of symptomatic CK elevations at doses from 5 to 40 milligrams is low and similar. The overall frequency increases to 1.0 percent at the 80-milligram dose.

However, many of these patients had symptomatic elevations related to causes such as heavy exercise or injury and many resolved on continued therapy at the same dose of rosuvastatin. If we exclude those cases with clearly identified other causes, we have left the cases with a more likely association to rosuvastatin therapy.

A total of thirteen possibly

treatment-related cases have been identified, one case each at 20-milligram and 40-milligram doses and eleven cases at 80-milligram dose. The one case observed at 20-milligram dose was in a patient who was also found to have a Coxsackie Type IV viral infection at the time of the event. Coxsackie Type IV viral infections have been associated with myopathy.

The patient at 40 milligrams had a history of asymptomatic CK elevations as high as 10,000 off statin therapy who had a CK elevation to 15,000 three days after initiating a weight-lifting program. Because the patient had associated arm pain, he was hospitalized to rule out a myocardial infarction. After ruling out for myocardial infarction and being discharged, the patient was restarted on rosuvastatin 40 milligrams and has now remained on this dose for several months and has been asymptomatic without CK elevations.

The eleven cases of possibly treatment-related myopathy at the 80-milligram gives a frequency of 0.7 percent at this dose. Importantly, all eleven of these patients recovered following discontinuation of therapy. Seven patients were hospitalized to receive intravenous

fluids. During the program, we also had two cases of myopathy observed in patients on simvastatin 80 milligrams which gave us a frequency of myopathy for that group of 0.4 percent. One of these patients was hospitalized to receive intravenous fluids.

[Slide.]

The eleven 80-milligram myopathy cases do allow us an opportunity to evaluate the possible risk factors for myopathy with rosuvastatin. The three major risk factors that we identified at the 80-milligram dose were age, renal insufficiency, and hypothyroidism. It is important to note that these are also identified as risk factors for myopathy with other marketed statins.

With regard to age, the frequency of myopathy was 0.2 percent in subjects less than 65 years old and 2.3 percent in subjects 65 years of age or older. Patients with a creatinine clearance less than 80 milliliters per minute had a myopathy frequency of 1.2 percent at the 80-milligram dose compared to a frequency of 0.2 percent in patients with a normal renal function or a creatinine clearance greater than 80 milliliters per minute.

However, whether renal insufficiency is

truly an independent risk factor for myopathy is difficult to determine from our data since we used the Cockroft Gault formula and age is a significant component in the creatinine-clearance calculation.

Although hypothyroidism was an exclusion criterion in our program, two patients with myopathy did have an elevated TSH at the time of their event.

With regard to gender, we did not find a sex-based predisposition to myopathy. However, of the seven patients hospitalized to receive intravenous fluids, five were females.

[Slide.]

The data from our program show that rosuvastatin was well tolerated from a skeletal-muscle perspective. An increased frequency of adverse skeletal-muscle effects compared to lower doses of rosuvastatin was observed at the 80-milligram dose. However, the vast majority of patients were safely treated even with the 80-milligram dose.

How do the skeletal-muscle data generated from this program compare to data for other statins? To look at this, we looked back at CK elevations greater than ten times the upper limit

of normal because this provide an objective measure for evaluating the potential for a dose of a statin to cause muscle toxicity.

In this slide, we compare the effects of rosuvastatin on this parameter to results reported for cerivastatin at 0.2 to 0.8 milligrams, pravastatin 40 and 80 milligrams, simvastatin, 40 and 80-milligrams, atorvastatin, 10 to 80 milligrams and rosuvastatin.

In this figure, we evaluate the overall benefits of a dose of a statin with regard to LDL-C lowering versus the risk of having a CK elevation greater than ten times the upper limit of normal. Note that at rosuvastatin doses up to and including 40 milligrams, the frequency of CK elevations is low and similar to that observed with other statins. Only at the 80-milligram dose where LDL-C is reduced 65 percent does the frequency of elevations increase above that observed for the highest doses of pravastatin, simvastatin, or atorvastatin.

Also observe the marked difference between rosuvastatin and cerivastatin where at 35 to 40 percent LDL-C lowering, the frequency of CK elevations is high.

One potential reason that the number of myopathies with cerivastatin was high is that a much larger percentage of hypercholesterolemic patients need LDL-C lowering in the range of 35 to 40 percent.

In order to get this lowering with cerivastatin, patients needed to be exposed to doses with a greater likelihood of affecting skeletal muscle.

[Slide.]

Overall, the skeletal-muscle data for rosuvastatin program show that it was well tolerated at doses up to and including 40 milligrams. At these doses, the frequency of adverse effects was similar to that observed for other marketed statins, but as you have seen in an earlier presentation, greater lipid modification can be achieved with rosuvastatin.

At the 80-milligram dose, patients achieved an additional 2 to 4 percent LDL-C reduction over the 40-milligram dose. However, the frequency of adverse skeletal-muscle effects at this dose increased above that observed for rosuvastatin 40 milligrams and the highest doses of other marketed statins.

Although a small number of patients

experienced adverse skeletal-muscle effects at the 80-milligram dose, many patients were safely treated. 1200 patients under the age of 65 were treated with the 80-milligram dose and the frequency of myopathy in this group was 0.2 percent. Importantly, all patients who had a significant adverse event at this dose recovered.

[Slide.]

I would now like to turn our attention to the effects of rosuvastatin on the kidney.

[Slide.]

Adverse statin effects on the kidney are well documented in terms of renal failure secondary to myoglobinuria associated with rhabdomyolysis. However, other potential effects on the kidney are not well documented. Following the completion of the initial Phase III studies for rosuvastatin, an increased frequency of proteinuria was detected predominantly at the 80-milligram dose.

In response to this finding, additional investigations were performed to characterize the frequency, magnitude, and nature of the proteinuria and to determine the potential for rosuvastatin to cause acute or progressive injury to the kidney. In this section, I will present the results of

these analyses.

[Slide.]

In the rosuvastatin program, proteinuria was evaluated primarily using dipstick testing. In the general population, a prevalence of proteinuria up to 10 percent on dipstick testing has been reported.

Proteinuria can have an organic etiology, such as that which occurs in patients with diabetes, hypertension, and urologic infections or it can be functional. Functional causes of proteinuria include exercise, orthostatic proteinuria, and proteinuria associated with pregnancy.

Proteinuria can occur due to changes in the glomerulus, the renal tubules or both sections of the nephron. The types of proteins excreted can help identify the source of the proteins.

Glomerular proteinuria is due to leakage of albumin and other larger molecular weight proteins through the glomerulus and is the type of proteinuria associated with diabetic kidney disease and hypertension.

Tubular proteinuria, which you will see is the pattern of proteinuria seen with rosuvastatin, is

due to reduced absorption of normally filtered low-molecular-weight proteins. The acute and long-term consequences of this type of proteinuria are less well defined and must be defined in the context of the drug or environmental factor causing the proteinuria.

[Slide.]

Shown here is Table 15 from the FDA briefing document. For comparative purposes, the data from the uncontrolled, open-label extension trials are omitted so that the pool only contains data from controlled clinical trials.

Presented in this table are the frequency of developing proteinuria at any time, hematuria at any time, or the combination of proteinuria and hematuria at any time for a given dose of statin. The data in the proteinuria column shows that the frequency of proteinuria for rosuvastatin at doses up to and including 40 milligrams is similar to that observed for comparator statins. However, at the 80-milligram dose, an increased frequency is observed.

The next column shows the frequency of hematuria with and without proteinuria. The frequency of hematuria with rosuvastatin ranged up

to 12 percent compared to a frequency of up to 8 percent on the comparator statins. Other evaluations, not shown here, have demonstrated that isolated hematuria is not associated with either rosuvastatin therapy or therapy with other statins.

The last column shows the frequency of proteinuria in combination with hematuria from the program. When comparing the data for rosuvastatin with the data obtained for other statins, we find an increased frequency of proteinuria/hematuria at the 80-milligram dose and possibly a signal at the 40-milligram dose. But note that, at the 40-milligram dose of simvastatin, we also see a frequency of 0.8 percent.

[Slide.]

The observation of an increased frequency of proteinuria and proteinuria in combination with hematuria predominantly at the 80-milligram dose led to a series of investigations to characterize the magnitude and nature of these findings.

First, we evaluated the patients with the most significant shifts from baseline in urine protein levels to determine the amount and types of proteins excreted. Shown in this table are total protein and albumin excretion normalized for

urinary creatinine excretion in patients with a shift from none or trace at baseline to 2-plus or greater levels of urine protein.

In these patients, the median protein excretion was only 0.6-milligram protein per milligram of creatinine. This value correlates to about 600 milligrams per day. Note that 150 milligrams of protein excretion per day is considered normal.

Of the total protein excreted, only about one-third was albumin. In disease states where the glomerulus is affected, the vast majority of urine protein excreted is albumin. Thus our, data suggested that the proteinuria was not glomerular in origin.

[Slide.]

Electrophoresis results and analyses of urinary proteins from patients who developed proteinuria showed that it was primarily tubular in origin. Our analyses showed that the proteins excreted were predominantly alpha-1 microglobulin, beta-2 microglobulin, and retinol-binding protein. These are proteins typically filtered at the glomerulus but normally reabsorbed at the level of the tubules.

Back-titration of patients in our program from 80 milligrams to 40 milligram allowed us another opportunity to assess the nature of the proteins in patients with proteinuria as well as the reversibility of the proteinuria. The data showed that at the 80-milligram dose, the greatest elevation in urine proteins was for low-molecular-weight proteins and that following back-titration to 40 milligrams, the greatest decrease was in these same urine proteins.

Our evaluation of hematuria in patients with proteinuria revealed that red blood cells were present on microscopic evaluation. Myoglobin levels were not elevated in these patients confirming that the hematuria was not secondary to muscle breakdown. Importantly, in our back-titration study, the combination of proteinuria and hematuria also reversed with back-titration.

Since the predominant effect observed with high doses of rosuvastatin was a tubular proteinuria, we performed a series of preclinical evaluations to explore a possible mechanism for the effect.

[Slide.]

I will start with the Preclinical data. Preclinical toxicology studies for the various statins show that all have tubular effects at very high exposure levels. However, in almost all of these animal models, the doses of statin leading to this effect also caused the animals to be moribund. Therefore, whether the effects are a primary effect of the statin or due to other secondary causes cannot be determined.

However, in one animal model, the cynomolgus monkey, the effect was observed at high doses of rosuvastatin and pravastatin, but the doses were not high enough to cause the animal to become moribund. The fact that the tubular toxicity was observed in animal models with all statins, that the types of proteins present in our clinical studies suggested a tubular proteinuria, and that these observations appeared to be dose related, led us to postulate that the proteinuria was due to an HMG-CoA-reductase inhibitory effect in proximal tubule cells.

To explore this hypothesis, we evaluated the effect of statins on albumin uptake in Opossum kidney tubule cells. This is a well characterized model for evaluating the potential effects of a

drug on renal tubules.

The results of the studies I am going to show you were later confirmed in a human renal-tubular-cell model.

[Slide.]

Shown in this figure is the effect of increasing concentrations of various statins on albumin uptake in the Opossum kidney cells. The statins that we are looking at are rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin. Note that with all of these statins, with increasing concentrations, albumin uptake is inhibited.

[Slide.]

The degree of inhibition is closely related to the degree of cholesterol inhibition in these cells. Note that once approximately 80 to 90 percent inhibition is observed, the percentage inhibition in albumin uptake begins to rapidly rise.

[Slide.]

To examine whether the observed effects were due to HMG-CoA reductase inhibition, we also examined the effects of adding mevalonate, the down-stream product of HMG-CoA reductase, to the

cells along with the statin.

This is the result of one experiment. The data show that the effects are consistent with an HMG-CoA-reductase inhibitory mechanism. The addition of mevalonate reverses the inhibition observed with simvastatin and rosuvastatin and this experiment has been repeated several times with different statins.

[Slide.]

Having explored a potential mechanism for the effect, we are still left with an important question. Why is proteinuria observed following therapy with high doses of rosuvastatin?

Two major characteristics of rosuvastatin help to address this issue, First, rosuvastatin is a highly effective inhibitor of HMG-CoA reductase. Second, approximately 28 percent of rosuvastatin systemic clearance is by the kidney, and this occurs predominantly by tubular secretion.

For other statins, the degree of renal excretion or the overall effectiveness in inhibiting HMG-CoA reductase is less than that observed with rosuvastatin.

[Slide.]

Although we have shown that the

proteinuria was predominantly tubular in nature and probably related to HMG-CoA reductase inhibition, the next important question to address is whether treatment with rosuvastatin leads to either short or long-term renal complications.

To address the issue of short-term or acute complications, we present here our cases of acute renal failure from our program. Out of the 12,569 patients treated with rosuvastatin in our program, eleven patients were reported to have acute renal failure, one case each at the 5, 10, and 20-milligram doses, two cases at the 40-milligram dose, and six cases at the 80-milligram dose.

For the five cases at doses below 80-milligram, none were attributed to therapy with rosuvastatin. Of the six cases at the 80-milligram dose, four of those were associated with myopathy. We are left with two cases of acute renal failure at the 80-milligram dose.

In these two patients on this dose, the etiology of the renal failure is unclear. Both patients had symptomatology suggesting a dehydrated state prior to the onset of renal failure and both had other comorbidities requiring treatment with

medications which could predispose them to renal failure independent of therapy with rosuvastatin.

These cases represent two cases out of 264 patients who initiated therapy at the 80-milligram dose and out of a total of 1583 patients treated with this dose. The current database contains over 4000 patients treated with rosuvastatin 40 milligrams of whom over 2000 initiated therapy with this dose. No cases of renal failure have been attributable to therapy with the 40-milligram dose of rosuvastatin.

Overall, the number of cases of acute renal failure observed in this program are not unexpected given the size of the current database with over 14,000 patient years exposure to rosuvastatin.

[Slide.]

Having shown that rosuvastatin is unlikely to cause acute or short-term detrimental effects on renal function at doses up to and including 40 milligrams, we next explored the potential for long-term treatment in patients with proteinuria and proteinuria in combination with hematuria to lead to decrements in renal function.

To do this, we used a creatinine elevation

greater than 30 percent as a marker for a potential renal effect. This is a sensitive marker and represents a level of change of about three standard deviations above the mean change in creatinine observed in our placebo group for our program.

In evaluating long-term effects, we once again to go our all Controlled/uncontrolled and RTLD data pool. It is, again, our largest pool of patients and includes patients with the longest durations of treatment with rosuvastatin.

This analysis includes patients who had a shift from none or trace proteinuria at baseline to 2-plus or greater proteinuria at the end of treatment. Using this level of change identifies subjects with a greater likelihood of developing treatment-related proteinuria and a level of proteinuria that should lead to changes in renal function if an association exists.

Note that similar to the previous analyses, the frequency of proteinuria was low and similar at rosuvastatin doses from 5 to 40 milligrams but increased at the 80-milligram dose. Of the patients who developed proteinuria, no patient had a 30 percent creatinine elevation at

the end of treatment at the 5-milligram, 10-milligram, or 40-milligram doses of rosuvastatin.

Two patients had an increase at the 20-milligram dose and eleven patients at the 80-milligram dose did have an elevation. Of these thirteen patients with elevations, only four patients had a 30 percent increase above the highest creatinine value observed during the pre-randomization period. All four of these patients were at the 80-milligram dose and two of the patients had myopathy. For the remaining two patients, the elevations were less than 0.5 milligrams per deciliter.

[Slide.]

If we now look at patients with proteinuria and hematuria, who represent a subset of the patients shown on the previous slide, we find similar results.

The data show that the number and frequency of patients with this finding is extremely low at doses up to and including 40 milligrams. An increased frequency is observed at the 80-milligram dose.

[Slide.]

An evaluation of patients treated for 96 weeks or longer gives additional information regarding the long-term effects of proteinuria. In this slide is shown information regarding proteinuria observed at any time, at the last visit, and the associated creatinine changes observed at the last visit.

The data show that the frequency of proteinuria observed at any time is greater than the frequency observed at the last visit at a given dose of drug. This suggests that although proteinuria can occur, in many patients it does decrease or resolve. This is demonstrated best in the 80-milligram group where the frequency at any time is 16.8 percent but decreases to 6.3 percent at the final visit.

The back-titration data, the greater than or equal to 40-milligram group, is also helpful because it contains important information in almost 800 patients, in over 800 patients receiving high doses of rosuvastatin. Note that the frequency of proteinuria observed at any time is similar to that observed at the 80-milligram group. However, at the last visit, in patients who are now almost entirely on the 40-milligram dose, the frequency of

proteinuria is similar to that observed with lower doses of rosuvastatin.

Out of 37 patients with proteinuria at the 80-milligram only eight had proteinuria following back-titration to 40-milligram demonstrating that proteinuria was reversible.

The creatinine data is also helpful. Note that no patients with proteinuria had a creatinine elevation greater than 30 percent at rosuvastatin doses up to 40 milligrams. Seven patients on 80-milligram had an elevation. In all seven of these patients, the elevation resolved on back-titration to 40 milligrams showing that the creatinine elevations, like the proteinuria findings were reversible.

[Slide.]

The results for patients with proteinuria in combination with hematuria, which is again a subset of the patients in the previous slide, showed similar results, no evidence for a treatment effect at rosuvastatin doses up to and including 40 milligrams. At the 80-milligram dose, both proteinuria and hematuria and the creatinine elevations were reversible on back-titration.

[Slide.]

In the FDA briefing document is a description of a patient who had an abnormal urinalysis with a creatinine elevation and a renal biopsy. The clinical course for this patient has relevance to the long-term safety of rosuvastatin and is presented on this slide.

The patient is a 69-year-old African male with a history of childhood renal disease, stasis ulcers, and back pain treated with aspirin, paracetemol, intramuscular penicillin injections, and topical steroids. At baseline, the subject had two urinalysis tests. One showed active sediment. The other showed 1-plus proteinuria without active sediment.

After 18 months, the subject had a serum creatinine measurement of 1.6 milligrams per deciliter from a baseline of 1.1 milligrams per deciliter. The urinalysis showed proteinuria and hematuria. A renal biopsy was performed which showed acute on chronic tubulointerstitial changes.

The laboratory abnormalities resolved following discontinuation of rosuvastatin, but proteinuria recurred upon rechallenges with rosuvastatin 80 milligrams and atorvastatin 40 milligrams. This case shows that proteinuria can

be observed with another statin if the patient is susceptible.

[Slide.]

Another method for evaluating the potential adverse effects of a drug on renal function is to evaluate the long-term effects of high-dose treatment in patients with baseline renal laboratory abnormalities since these patients might be expected to show a greater susceptibility to adverse renal effects of drugs.

In this slide, we compare the effects of treatment with at least 40 milligrams of rosuvastatin for greater than or equal to 96 weeks in patients with normal and impaired renal function. Note that, in general, serum creatinine levels tended to decrease in all groups and the percentage of outliers was similar in patients with normal or impaired renal function.

[Slide.]

In summary, we have carefully evaluated a proteinuria and proteinuria/hematuria signal with regard to frequency, magnitude, nature, and the potential for rosuvastatin to cause acute or long-term renal parenchymal damage.

Our data shows that dipstick positive

proteinuria, primarily tubular in origin, was observed predominately at the 80-milligram dose. In a small percentage of patients, this finding was associated with microscopic hematuria. The data show that the finding was transient in many cases, reversible and not associated with long-term detrimental effects on renal function. Although two cases of renal failure had a temporal relationship to therapy with the 80-milligram dose, both of these cases had other identifiable causes. At doses up to and including 40 milligrams, rosuvastatin was well-tolerated from the renal perspective.

An important question to address is whether the prescribing information for rosuvastatin should include renal monitoring. As shown by the data, routine urinalysis or creatinine monitoring is not necessary. The data show that treatment wit rosuvastatin at doses from 5 to 40 milligrams does not result in acute or long-term adverse effects on renal function. Even at the 80-milligram dose, any changes that were seen were reversible with back-titration or stopping therapy, so even at this dose, there is no evidence of a long-term irreversible effect on renal function.

[Slide.]

Having now reviewed our clinical safety database, I would like to speak to the last objective that we set for our program, to determine whether rosuvastatin would have a low potential for significant drug-drug interactions.

In this regard, I will present the results of our drug interaction studies in the following areas; interactions with drugs that are metabolized through interactions with cytochrome P450 isoenzymes or PgP transporters and interactions with drugs known to result in an increased potential for myopathy. in particular, cyclosporine and gemfibrozil.

[Slide.]

Our drug interaction studies with the cytochrome P450 3A4 inhibitors, ketoconazole and erythromycin, show that rosuvastatin is not metabolized by this route. No effect on rosuvastatin AUC was observed with ketoconazole, and with erythromycin, a clinically insignificant 0.2-fold decrease in AUC was observed.

Interactions with these same two drugs along with the results of the digoxin-interaction study also show that rosuvastatin does not interact

with PgP transporters.
Finally, the result of the fluconazole interaction study shows that rosuvastatin is not metabolized by cytochrome P450 2C9 or 2C19.

[Slide.]

I would now like to address the issue of interactions with cyclosporine and gemfibrozil. Our drug-interaction study with cyclosporine revealed a 7.1-fold increase in rosuvastatin plasma concentrations.
Shown in this figure are the results for rosuvastatin compared to data reported for other statins in the literature. The results for rosuvastatin are similar to the other statins except for lovastatin, which appears to have the largest interaction.

Based on the 7.1-fold increase in rosuvastatin AUC, the dose of rosuvastatin should be limited to 5 milligrams when used in conjunction with cyclosporine.

[Slide.]

Shown next is our drug interaction study with gemfibrozil. In this trial, a 1.9-fold increase in rosuvastatin AUC was observed. This increase was similar to that reported for

simvastatin, lovastatin, and pravastatin but less than the interaction observed with cerivastatin. Once again, based on the level of increase in AUC and the known risk for myopathy when statins are co-administered with gemfibrozil, the dose of rosuvastatin should not exceed 10-milligram in this population.

[Slide.]

Because of the increasing use of other fibrates, we performed a drug-interaction study with fenofibrate. As opposed to the 1.9-fold increase in AUC observed in the gemfibrozil interaction study, no interaction was observed when rosuvastatin was co-administered with fenofibrate.

[Slide.]

Our drug interactions studies show that rosuvastatin will have a low potential for significant drug interactions. However, other factors besides drug interactions may impact exposure to rosuvastatin and could therefore impact on safety. Data from our clinical pharmacology program revealed that systemic exposure to rosuvastatin was not affected by age, sex, or the presence of mild to moderate renal impairment.

In patients with severe renal impairment,

rosuvastatin plasma concentrations increased approximately 2 to 3 fold. Based on these findings, we propose that the dose of rosuvastatin is limited to 10-milligram in this population. Rosuvastatin plasma concentrations were also increased in patients with severe hepatic impairment. Note that, similar to other statins, rosuvastatin is contraindicated in patients with active hepatic disease.

Pharmacokinetic evaluations were also performed to assess effects based on ethnicity. We did find that exposure to rosuvastatin was increased approximately 2-fold in Japanese patients in Japan. However, we do not know whether this was due to environmental or genetic factors. Importantly, no differences in exposure were observed among Caucasians, Black, or Hispanic patients.

[Slide.]

This morning, I have reviewed for you the safety results from our program. In this program, doses of rosuvastatin up to and including 80 milligrams were thoroughly explored in over 12,500 dyslipidemic patients. This is the largest NDA ever submitted for a statin.

This program was inclusive. Approximately one-third of the patients were 65 years or older and a high percentage of patients had co-morbidities such as hypertension, diabetes, renal insufficiency, and atherosclerosis.

The data show that within the proposed 5-milligram to 40-milligram dose range, the safety profile of rosuvastatin was similar to other marketed statins.
At the 80-milligram dose, the frequency of adverse skeletal-muscle and renal effects increases above that observed for currently marketed statins.
However, even at this dose, the majority of patients were safely treated. Importantly, all patients with an adverse event at the 80-milligram dose recovered.

We have also demonstrated that rosuvastatin will have a low potential for significant drug-drug interactions.
For those patients at risk for significant adverse events due to drug interactions, our proposed labeling will reflect the necessary information.

[Slide.]

Having now reviewed the overall safety database, the issue of selecting appropriate doses

of rosuvastatin to market involves weighing the potentials risks of a dose versus the potential benefits afforded by its use.

A rosuvastatin 10-milligram to 40-milligram dose range is appropriate for the general population of patients with dyslipidemia.

Our data which clearly demonstrate the excellent lipid modifying benefits of the proposed 10-milligram to 40-milligram dose range at both the starting dose and across the dose range compared to other currently marketed statins.

Also, within the proposed dose range, rosuvastatin brings a high percentage of patients to recommended NCEP lipid goals.

[Slide.]

Why is a 10-milligram start dose appropriate for the general population of patients with dyslipidemia?

The reason is once again the overall favorable benefit to risk of this dose.

Our data shows that the 10-milligram dose provides additional lipid efficacy compared to the 5-milligram dose, without showing a difference in overall safety. As previously stated, for patients on cyclosporine, a 5 milligram dose is available.

[Slide.]

And last, why is a 40-milligram dose an appropriate top dose for patients with dyslipidemia?

First, our data show that the 40-milligram dose of rosuvastatin provides additional lipid-modifying benefits compared to the 20-milligram dose.

With regard to safety, our program has evaluated rosuvastatin at doses up to and including 80 milligrams. Doing this has allowed us the opportunity to understand our drug and the potential risks associated with its use.

The 40-milligram dose was studied in over 4000 patients with a demographic similar to that of the 80-milligram group. Over 2000 subjects initiated therapy at this dose. Our data clearly show that this dose was well-tolerated.

Adding to the favorable benefit to risk profile for this dose is the fact that this is not a recommended starting dose. The 40-milligram dose is for those patients who do not achieve the necessary lipid-modifying effects at the 20-milligram dose of rosuvastatin.

So, in summary, using 40-milligram as the top dose for rosuvastatin will provide an overall

rosuvastatin dose range, which is safe and provides additional lipid-modifying benefits over current statin therapies.

I would now like to introduce Dr. Daniel Rader from the University of Pennsylvania who will briefly discuss the potential role of rosuvastatin in the treatment of dyslipidemic patients.

Dr. Rader.

The Role of Rosuvastatin
in the Treatment of Dyslipidemia

DR. RADER: Thanks very much.

[Slide.]

I am Dan Rader. I direct a preventive cardiology program at the University of Pennsylvania in the Lipid Clinic there. I do research in lipids and atherosclerosis and I see patients with lipid disorders. I am happy to be here today to present to you my thoughts, briefly, on the potential role of rosuvastatin in the treatment of dyslipidemia.

[Slide.]

I would like to start again by reminding you, and I think you all know at this point, that we have had a major evolution in the Lipid Management Guideline from 1988 to the most recent

ATP-3 Guidelines in 2001. These guidelines have been reflected by increasing aggressiveness of cholesterol-lowering therapy from initially a focus on non-statin therapy to, most recently, because of the more aggressive guidelines, a focus on high-dose statins and combination therapy in order to be able to achieve the kinds of aggressive targets that are recommended in these guidelines.

I would like to point out that Dr. Don Hunninghake, who is here with us today, has been part of the NCP from the beginning and, in fact, chaired the Drug Therapy Section for all three of the adult treatment panels. So any questions you have about NCP, we will certainly forward to Don.

[Slide.]

What I would like to do so sort of set the stage and explain to you why I think rosuvastatin is an important addition to the therapeutic armamentarium for dyslipidemia is really to point out that, in fact, we have difficulty achieving goals in a lot of our patients with dyslipidemia.

To go back to data that is really based on the ATP-2 Guidelines, this slide reflects four different studies, all performed in the mid- to late-90's and published between '99 and 2001 really

asking, in an observational sense, how well were we doing in terms of getting patients to the ATP-2 goals.

I will just point out here that even the low-risk patients on the left, only about two-thirds of them were at goal. The medium-risk patients in the middle, only about a third were at goal. The high-risk coronary heart-disease patients who need to be targeted to LDLs less than or equal to 100 by these guidelines, only about a fifth to a quarter were at goal. So, clearly, at that time, many patients were not at goal.

Now, you might ask, maybe patients are not being treated or maybe they are not being appropriately titrated and maybe many of them are just almost at goal but not quite. But, in this study, one of those four studies, the L-TAP Study directed by Dr. Tom Pearson, who is also here with us today, really shows that that is not the case. In fact, in L-TAP, a lot of the patients who were not at goal were actually quite far from goal.

Note that on the right a full l6.6 percent of the patients, nearly as many as were at goal, as shown at the left, were over 160 milligrams per deciliter, far from their goal of 100 and 45

percent of the patients in L-TAP who needed to be targeted to LDLs less than 100 were actually over 130. So I think this demonstrates that it is not just in terms of getting people to goal, that we are getting almost there but not quite there.

A lot of people have a long way to go before they actually get their NCP goals.

[Slide.]

This is a study by Ross Simpson and his colleagues that looked, in a real-world setting, at following nearly 3,000 patients asking what is actually happening in these high-risk patients who need to be targeted to LDLs less than 100. You can see that, among these patients, when they were started on a statin, 47 percent, shown on the right, got to goal at the starting dose. But over half did not get to goal at starting dose.

I think this is an important point. Many patients don't get to goal on starting doses of statins. Of that group of patients, 47 percent were titrated but more than half were not titrated, again reflecting an important point. Physicians often don't appropriately titrate patients to get them to goals.

Finally, I think perhaps most importantly,

among the patients who were titrated, only one-third of those patients actually got to goal. So even among titrated patients, two-thirds of the patients did not actually get to goal. I think this illustrates, and is something I am going to come back to, it is actually difficult to get many patients to goal even with appropriate titration.

[Slide.]

This is recent data. This came out in Circulation a few months ago from the NHANES Study. This is data collected between 1999 and 2000 so it really reflects treatment in the modern era with all the current statins that we currently have on market.

There is a lot of data in this report but I just thought I would focus on one key issue which is only 47 percent of the hypercholesterolemic patients who were being actively treated with drug actually were adequately controlled. So I think, again, this suggests that yes, failure to treat is a problem but even among treated patients, failure to actually get adequate control and treat patients to goal is a real issue.

Now, maybe it is just that patients are not being titrated appropriately. Certainly, that

would be a reasonable question to ask. But I want to bring you back again to this study directed by Dr. Christie Ballantyne who is also here with us, a ACCESS Study, which took hypercholesterolemic patients, randomized them to five different statins and then titrated as needed to get to goal.

You will see again that, for LDL goals, even patients randomized to atorvastatin titrated as needed up to a maximum of 80 milligrams, only a little over 70 percent of these patients actually got to goal of LDL less than 100. For HDL cholesterol, which, in general, is even harder to reach, only about 60 percent of the patients on the atorvastatin arm got to goal.

So you can see that even when appropriately titrated in a controlled setting like this trial, it is difficult to get many patients to goal.

[Slide.]

I have been focusing on our current goals but I do have to tell you that, in the lipid field, many of us feel that our current goals may not be aggressive enough. I am going to show you two slides that kind of address that issue. One is this slide that really plots the on-treatment LDL

cholesterol levels on follow up in all the big statin trials on the x-axis and the percent with coronary heart-disease events on the y-axis.

You will note that, for both secondary prevention and primary prevention, there seems to be a clear linear relationship between the on-treatment LDL cholesterol level and the percent with coronary events. This is, admittedly, a crude way to look at this but I think it gives us some idea of this relationship.

I also want to point out that there are two studies on this slide; the Heart Protection Study, HPS, and the ASCOT Study that came out since the ATP-3 Guidelines. So we have new data coming out even since those guidelines that address this issue of, perhaps, maybe even lower targets would be appropriate.

You will note that, in both of those studies in the treated groups, the LDL cholesterol levels in the treated group, the mean level, was well less than 100.

[Slide.]

I wanted to actually explore the Heart Protection Study in just a little more detail with this slide. I think this is really quite important

for this concept of should we be treating people even lower. So the Heart Protection Study enrolled people almost regardless of their cholesterol levels.

I just thought I would show you this analysis that the investigators did where they looked at baseline LDL cholesterol by tertile. You will note, in the highest tertile group, where the mean LDL cholesterol was about 140, treatment with simvastatin lowered LDL to a little over 100 and lowered cardiovascular events as you can see here.

In the lowest LDL tertile in this group, the mean LDL was slightly less than 100 at baseline and you can see that treatment there lowered LDLs into the 60s and also significant reduced risk. Of course, we don't really know, if we took everybody and lowered their LDLs into the 60s, whether we would see even greater event reductions than we see in the current statin trials.

But I think, based on data like this, many of have concluded that the guidelines are very likely to become more aggressive with regard to the need to treat LDL. Certainly, speaking for myself, based on data like this, I treat my high-risk patients, patients with coronary disease and

diabetes, somewhat more aggressively than just targeting 100. I think I would really like to see the LDLs even lower.

I think you can imagine, as our targets get even lower, as our practice gets even more aggressive, it is going to be even harder to target patients appropriately to these goals. So I would suggest to you that, in fact, despite all the good drugs that we have on the market, there is still a medical need in treatment of dyslipidemia. There is a need for more efficacious therapy to achieve a few different goals, one of which is greater LDL and non-HDL cholesterol-lowering at the start dose.

I have already explained to you how many patients don't get to goal on start dose and, unfortunately, many physicians don't appropriately titrate.

[Slide.]

I thought I would show you just one slide with a little bit of sort of composite data that really addresses direct head-to-head comparisons of rosuvastatin at its 10-milligram start dose with commonly used start doses of other statins. So these two panels can't be compared with each other.

They are really self-contained but if you look at the left, these are three different trials, Trials 24 to 26, comparing rosuvastatin 10 milligrams to atorvastatin 10 milligrams in a head-to-head comparison.

What I have selected to show you here is actually the achievement of both the LDL cholesterol and the non-HDL cholesterol goals, really the ultimate goal of the ATP-3 guidelines. You should be targeting both of these. You can see that rosuvastatin 10 brought substantially greater number of patients to this combined goal than atorvastatin 10.

Shown on the right, Trials 27 and 28, involved direct head-to-head comparisons of rosuvastatin 10 with simvastatin 20 and pravastatin 20. Again, you see significantly greater bringing patients to this combined LDL and non-HDL goal with rosuvastatin 10 compared to the other two statins.

So I think it is safe to say that use of rosuvastatin 10 milligrams will bring a greater number of patients to NCP goals and, I would suggest to you, could have substantial public-health benefit with regard to that.

[Slide.]

Now, I think the second need for more efficacy therapy in treatment of dyslipidemia is clearly to achieve greater LDL and non-HDL cholesterol lowering at maximal dose. We really need therapies that will get our difficult-to-treat patients down closer to the goals that we need to treat these patients to.

[Slide.]

Now, to illustrate this point, I would like to just briefly bring up familial hypercholesterolemia. The heterozygous form of this condition is common. There are about 500,000 patients in the U.S. with heterozygous FH for a frequency of about 1 in 500, more common, I believe, than Type 1 diabetes, for example.

FH is a serious disease. Even with treated with our current drugs, the average age of onset of coronary disease is about 45 to 50 in men and about 55 to 60 in women and it is difficult to treat. As I will show you in a second, most FH patients cannot be adequately treated to NCP goals using our current therapies.

[Slide.]

In this slide, what I decided to do is show you two different studies. These are two

independent studies both in heterozygous FH patients, both directed by Dr. Evan Stein, who is actually here with us today as well. One is a study that you have already seen from Dr. Blasetto on the left, but I just kind of encapsulated it here, looking at rosuvastatin 40 milligrams and atorvastatin 80 milligrams in these high-risk FH patients who are being targeted to LDL less than 100.

You can see that the rosuvastatin, as you saw previously, got substantially more of these high-risk FH patients to goal.

On the right, for comparison or to flesh out this concept, I show you another study directed by Dr. Stein that compared atorvastatin 80 milligrams, so the same comparator, to atorvastatin 40 milligram plus ezetimide, 10 milligrams. You will note that, although these are different studies in different populations both involving over 600 patients, by the way, you will note that the atorvastatin 80 performed about the same. Only about 4 percent of these high-risk FH patients got to goal, and the combination of atorva 40 plus ezetimide got, again, about 17 percent of the patients to goal.

So I think the main point here is rosuvastatin 40 does do better than any other single monotherapy statin that we have on the market in terms of treating these difficult-to-treat patients. But note that still less than one in five patients are getting to goal.

So I think clearly, with this type of severe hypercholesterolemic patient, the future is being able to use rosuvastatin 40--we really need that dose for these patients--and then adding on combination therapies including the additional of ezetimide to the rosuvastatin 40 to try to get more of these patients to goal.

[Slide.]

I would like to turn for a minute to HDL. HDL is a common condition, low HDL, and represents an important medical need. It is one of the most common risk factors in patients with coronary disease. ATP-3 importantly placed new emphasis on low HDL as a risk factor and as a potential target for intervention.

Data are increasingly suggesting that even modest increases in HDL may translate into substantial cardiovascular risk reduction. So I would like to suggest that, in fact, another need

in treatment of dyslipidemia is getting better at raising HDL cholesterol.

[Slide.]

Dr. Blasetto already showed you data from the STELLAR Trial looking at the comparison with rosuvastatin with other statins in terms of HDL. I thought what I would show you here is looking at the same trial but asking the question what did rosuvastatin do in terms of raising HDL in a low-HDL group, people with HDLs less than 40.

You can see here on the left that the HDL raising in this subgroup with rosuvastatin was between 12 and 20 percent. So HDL raising certainly compares favorably to the best HDL-raising drugs we currently have on the market.

[Slide.]

Admittedly, it is difficult to predict what incremental reductions in LDL and incremental increases in HDL will do in terms of reduction in cardiovascular risk. But the NCP and the ATP-3 report did make these following estimates based on observational studies as well as the randomized controlled trials that we have available, and that is that, for every 1 percent decrease in LDL cholesterol, there would be expected to be a

reduction of coronary heart-disease risk by approximately 1 percent and that, for every 1 percent increase in HDL cholesterol, there might be expected to be a reduction in coronary heart-disease risk by about 3 percent.

So I think you can imagine that if, in fact, these do hold true, that even incremental further reductions in LDL, further increases in HDL, could, in fact, translate into substantial further risk reduction for the patient.

[Slide.]

So, in summary, I suggest to you that there is a role for rosuvastatin in treatment of dyslipidemia, that, first of all, the greater LDL cholesterol and non-HDL cholesterol lowering at the start dose will, in fact, bring more patients to goal at start dose and I believe have public-health benefits as a result.

Second, the greater LDL cholesterol and non-HDL lowering at the maximal dose of 40 milligrams will make it easier for us to treat our patients with FH, other forms of severe hypercholesterolemia, diabetics, many of whom are also difficult to treat, and I would suggest to you that we really do need this 40-milligram dose to

more effectively treat these patients.

Finally, the HDL raising of rosuvastatin, although incremental, certainly would be suggested to result in increased reduction in cardiovascular events as well.

So, in summary, I would suggest to you that, in fact, rosuvastatin does provide an important and valuable addition to the therapeutic armamentarium for the treatment of dyslipidemia.

Thank you very much.

DR. BRAUNSTEIN: Thank you for a lovely comprehensive overview.

We will now take a fifteen-minute break and reconvene at 10:45 for questions from the committee to the sponsor.

[Break.]

Questions from the Committee

DR. BRAUNSTEIN: We will open up the session for questions and answers from the committee. The committee will also have an opportunity for questions, both the FDA and the sponsor, following the FDA's presentation. But now we will restrict ourselves to sponsor's presentation.

Questions? Dr. Hennekens?

DR. HENNEKENS: I was extremely favorably impressed with the size and scope of this development program as well as the comprehensive presentations. Dr. Orloff, in his comments, gave us some two focused sets of charges that, perhaps, might merit further consideration. One was he spoke of perhaps the need for further safety data directly comparing the 20 and 40 milligrams at the 40-milligram start dose and talked about 600 patients or more. Secondly, further clarification of the new onset of proteinuria directly at the 20 and 40-milligram doses, Dr. Hutchinson's Slide CS24, if taken at face value, suggested that those rates were 0.3 at 20 and 1.3 percent at 40 which, if real, would be a relative risk of 4.3.

So, perhaps, further clarification of those two issues might be helpful in our deliberations, either now or sometime during the day.

DR. BRAUNSTEIN: Do you want to respond to that?

DR. HUTCHINSON: Just to clarify your question, Dr. Hennekens, you are interested in the frequency--

DR. HENNEKENS: The second part related to

your presentation was from your Slide CS34.

DR. HUTCHINSON: Yes; the FDA's analysis of our data.

[Slide.]

DR. HENNEKENS: Yes. If you look at the right-hand column for the 20 versus the 40-milligram dose, it was 0.3 to 1.3, just further clarification of that would be helpful to me.

DR. HUTCHINSON: If I can show you the data from our largest pool of patients which will give you a better feel for the overall frequency of proteinuria-hematuria in our program, I may be able to address your specific questions.

[Slide.]

This was data that was presented during my presentation. Now, this takes all patients in our program that had urinalysis and creatinine measurements. It looks at what happens in patients with the most significant degrees of change regarding proteinuria and hematuria from baseline and then what happened in those patients at the end of treatment with regard to creatinine changes.

As you can see, the percentage of patients that had proteinuria along with some level of hematuria ranged from 0.10 to 0.2 percent at doses

up to 40 milligrams. We see an increased frequency of this finding at the 80-milligram dose.

What is critical here is to know whether or not this finding is associated with any effects on renal function so we use this sensitive marker, which is creatinine elevations greater than 30 percent, to evaluate whether or not the proteinuria and the hematuria that was there had an effect on the kidney.

As you can see, 0, 0, 1, 0, 8. When we go back and evaluate these patients because, in our program, what we use for creatinine baseline was the value of creatinine closest to Week 0. However, a number of these patients had multiple baseline creatinine measurements.

This identified a group of nine patients. If you go back and evaluate those patients, what you find is that, in almost all cases, what happens here is that the patients don't even have an elevation in creatinine greater than 30 percent of the maximum value observed the baseline. In the few numbers of patients, the one or two patients that do have an elevation, the creatinine elevation in these patients is less than 0.5 milligrams per deciliter.

We do have, in a couple of these patients also follow up after discontinuation of therapy. Following discontinuation of therapy, what happens is that creatinine elevation resolved in those patients where we had follow up.

I think the 96-week data which looks at proteinuria, hematuria and the creatinine elevations also gives you some important information here as well. These are patients that are going to be exposed for a mean of 2.4 years with our drug.

[Slide.]

Here in these patients we are once again looking at this combination of proteinuria and hematuria to determine whether or not it was associated with any change in serum creatinine, this 30 percent marker. Just to give you an idea if somebody had a creatinine change from 0.6 milligrams per deciliter to 0.8 milligrams per deciliter, they would fulfill this criterion.

But, if we look at this, what we find, first of all, after 96 weeks, we had one patient in the 40-milligram dose group that met this criterion, one patient at the 10-milligram group. If we look for creatinine increases, we find that

none of these patients had a creatinine increase. We see that, at 80 milligrams, five patients had an increase but, in our program, because we back-titrated patients from 80 to 40 milligrams, we had the opportunity to follow many of these 80-milligram patients longer term.

What we find is that, in these patients once they get back-titrated, look at the frequency of proteinuria and hematuria. It now approximates what we see at very low doses of rosuvastatin. These are patients receiving high doses. Importantly, those five creatinine elevations are gone.

So, from our patient, we have a very large dataset. We have a very large dataset in general looking at the 5, 10, 20, 40, and 80-milligram doses. I think we have provided very good data to show what the estimates of this finding will be at the various doses and we have also provided very substantial data regarding what the short and long-term consequences of the findings are.

What we have found is that, in general, transient, reversible, not associated with any effects on renal function and, at the same time, that 40-milligram dose is giving patients

additional significant LDL-C reductions which provide value.

DR. BRAUNSTEIN: Could you explain what the difference is between your table that you just showed and Table 15 from the FDA? I know there are minor differences in numbers of patients but it was 1.3 versus--you had 0.2 percent up there and they had 1.3. So why the difference?

DR. HUTCHINSON: The difference is simply the type of evaluation that was done. In the FDA evaluation, we are looking here at proteinuria, hematuria and the combination at any time during the program. So this takes into account if someone had proteinuria at Week 2 but didn't have anything at the end of the day, they would get picked up in this analysis.

It is a very good analysis if you want to look for potential signals. But if you want to evaluate what is happening with regard to renal function, you need to follow these patients out long-term and see what occurs. That is the analysis that I followed up with.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: Can you put those back?

DR. HUTCHINSON: Yes.

DR. WOOLF: Sort of following up on the same issue, what is the time course of the development of proteinuria and hematuria? Is it seen within a few weeks? Is it seen in a few months? You talked about the etiology of proteinuria but not of the hematuria. Do you have any idea where that is coming from?

Then I have a final comment about your suggestion about not really--a recommendation that we do not need to put I guess the term is a "warning" in the labeling about monitoring for proteinuria.

DR. HUTCHINSON: Several questions to address here.

DR. WOOLF: Time course, etiology.

DR. HUTCHINSON: Yes; time course, first. Thank you very much. With regard to time course, you can see that proteinuria occurs as early as two weeks following treatment. We observed this predominantly at the 80-milligram dose. However, proteinuria can occur later. But the tendency for the proteinuria, as I showed you with the 96-week data, is for the proteinuria, should it appear, to resolve. But it can occur as early as two weeks.

Now, the second question was with regard

to the hematuria. With regard to the hematuria, we don't have an explanation for the hematuria. If I can please see the Trial 99 table from the FDA document, that does address, in some respects, the hematuria.

[Slide.]

In response to our earlier findings from the program, we went forward and did a prospective study looking at rosuvastatin 40 milligrams versus simvastatin 80 milligrams to try to characterize the frequency of this finding in other statins and also to understand a little bit about what was happening with the proteinuria, proteinuria-hematuria.

This study did not have a placebo lead-in, a placebo treatment arm, but there was a dietary lead-in, a six-week dietary lead-in period. During that time period, patients had one or two urinalysis samples. They were off statin therapy.

As you can see, during this time period, we had a 3.4 percent frequency of proteinuria. The proteinuria greater than 2-plus was 0.6 percent and hematuria greater than 1-plus was 7.9 percent during this period.

Following treatment with simvastatin 80

and rosuvastatin 40, we find that hematuria, it was roughly similar in both of the treatment groups. We do see a suggestion, however, that there tended to be slightly more proteinuria with rosuvastatin.

We are not completely clear on where the hematuria is coming from with regard to the proteinuria-hematuria potentially seen with rosuvastatin, particularly at the 80-milligram dose. What we know about the proteinuria-hematuria is it seems to follow the same type of course as the proteinuria does, which is it is transient, resolves with back-titration from 80 milligrams to 40 milligrams and, once again, not associated with any acute or long-term effects on the kidney.

DR. WOOLF: Then, in regards to your suggestion about the labeling, you have roughly 100 patients who have been followed on a 40-milligram dose for, I think you said two-and-a-half years.

DR. HUTCHINSON: Yes.

DR. WOOLF: One of whom developed hematuria-proteinuria. We are talking about patients who are going to be on this essentially for a lifetime. While two-and-a-half years is rewarding, a lifetime is, hopefully, a lot longer than that.

If you don't monitor for it, you will never be able to know that it disappears when it--to back-titrate. So it is non sequitur. You have to monitor to able to know that you have to do something about it. So, to me, it is a disconnect.

DR. HUTCHINSON: That's true if you are using the 80-milligram dose. However, we are not suggesting that we are going to be treating patients with the 80-milligram dose. Now, you say 100 patients, but if I can please see the 96-week data again, because it is not really just 100 patients that we looked at in this program.

People were not dropping out of our program because of proteinuria and because of increased creatinine. So we had the opportunity to follow these patients long-term.

[Slide.]

If we look at the 96-week data, which I showed earlier, you are talking about 761 patients. We are also talking about over 1,165 patients in our program that have been exposed to doses greater than or equal to 40 milligram for 48 weeks. So, again, it is not only 100 patients. It is over 1,000 patients.

DR. WOOLF: At the 40-milligram dose, it

is 100.

DR. HUTCHINSON: At the 40-milligram dose, here, that have never been exposed to the 80-milligram dose; correct. It is 100. But, once again, if this drug was causing significant effects on the kidney, one would expect that what we are seeing at 80 milligrams, you would expect to see the residual of that effect once you drop these patients back to 40 milligrams.

We don't see it. In fact, the frequency of the finding approximates the lower dose. So, with regard to monitoring, you are dealing with patients with atherosclerosis, diabetes, hypertensions. These people have fluctuations of 30 percent in creatinine that can occur at almost any time.

It is more likely that they will get a fluctuation of 30 percent in their serum creatinine from the other medications that they are on or their disease than they will due to rosuvastatin or another statin.

DR. BRAUNSTEIN: Dr. Follman.

DR. FOLLMAN: I would like to make a comment about reversibility. I think it will be easiest to make this comment if you bring up Slide

CS35.

[Slide.]

I think that is not the one I want but I think I can make the point with this anyway. When were are looking proteinuria and hematuria and so on, these are parameters that will wax and wane with time with biological processes that the patients are undergoing with measurement error and who knows what. So, if you look over the course of the trial and say, "Oh; I have a high rate of proteinuria," and then you look at the very last visit and note that it is lower, to what extent is that evidence of reversibility or to what extent is that evidence that you have a biological process that fluctuates some.

So to really sort that out, you would need a control group in some way. So this relates to your comments when you say when you back-titrate I think from 80 milligrams to 40 milligrams amongst those who had proteinuria, the rate went down.

Once again, I would like a control group to really feel comfortable that this is evidence primarily of reversibility rather than just fluctuations where you happen to catch them when they had proteinuria and then, when you

subsequently measure it one more time, it is gone.

So we would like to believe that is evidence of reversibility, I think. But we just can't really conclude that without a control group.

DR. HUTCHINSON: Let me show you some data from a substudy that we performed in one of our open-label extension trials where we took patients that were on the 80-milligram dose and, when we were back-titrating these patients, we performed very careful timed urine measurements as well as other analyses in these patients.

DR. FOLLMAN: So this is where the group as a whole is back-titrated at basically a fixed point in time?

DR. HUTCHINSON: This is within four weeks of back-titration of patients from 80 to 40 milligrams.

DR. FOLLMAN: What was the reason for back-titration? Was it based on the patient's evidence of proteinuria or clinical characteristics?

DR. HUTCHINSON: Not at all.

DR. FOLLMAN: So it was done to everyone?

DR. HUTCHINSON: This was done to everyone in the program because we had looked carefully at

our 80-milligram data and it felt, at that time, that the efficacy that we were getting did not justify its use in the general population because of some of the adverse events we were seeing.

However, this is very strong evidence here that the proteinuria was reversing. These are patients on rosuvastatin 80 milligrams with proteinuria. These are patients with elevated urinary total proteins when they are on the 80-milligram dose and subsequently back-titrated to 40 milligrams. This is four weeks later.

DR. FOLLMAN: This is the whole group?

DR. HUTCHINSON: This is not everyone on 80. This is done in selected sites. The reason it had to be done that way is because we were doing careful timed urine collections as part of the study.

I will show you the whole group in a second.

DR. FOLLMAN: Okay.

[Slide.]

DR. HUTCHINSON: But, in a very careful evaluation of these patients, you see that going from 80 milligrams to 40 milligrams, we get a substantial reversal and decrease in the

proteinuria so, once again, suggesting that the proteinuria was resolving.

[Slide.]

Now, if we take the patients overall, and there are 752 patients back-titrated here, from 80 milligrams to 40 milligrams, we see that the frequency of 1-plus or greater proteinuria goes from 12 percent down to 4.8 percent and greater than or equal to 2-plus 7.5 percent down to 1.9 percent.

With regard to proteinuria-hematuria, 21 out of 46 of the patients here at a urine protein dipstick blood greater than or equal to 1-plus. 20 of the 21 no longer had that combined effect at four weeks after the back-titration, once again showing the reversibility, showing this goes away.

DR. FOLLMAN: Did you do the previous slide in all the patients, the one with the figure where you showed it went down nicely? It seemed that that was in the selected group that had high protein, high urinary protein--

DR. HUTCHINSON: This one was in patients with elevated urinary total protein.

DR. FOLLMAN: So, once again, this is not surprising to me that there would be a tendency for

it to go down. Once again, I want to sort out the reversibility versus just fluctuations going down. You select them with high values, look at them again, and they go down.

DR. HUTCHINSON: I believe what we need to look at is the totality of the data here. This signal is not seen in a lot of people, first of all. It is seen predominantly at the 80-milligram dose. We were not going to be treating patients any longer with the 80-milligram dose so, in order to be able to do these types of evaluations, these patients provided a very nice cohort to study and we used them to study the reversibility of the phenomenon.

What is very important here is the consistency of the findings. The key issue here is if proteinuria or proteinuria-hematuria is important from the standpoint of causing an effect on renal function, then, certainly, the patients that had the greatest levels of proteinuria and proteinuria-hematuria and have it for the longest duration, which would potentially be those with it at the end of the day, would be the most likely group to have a creatinine elevation if an association existed.

But what is amazing here is, out of the thousands of patients in the program, you evaluate these people and then you come down with one or two people at up to 40 milligrams and a handful at 80 milligrams. When you back-titrate the patients on 80 milligrams, the findings seem to reverse.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: Related to the same issue, it seems that the concern that the proteinuria is trying to predict is the concern of progressive loss of creatinine clearance. We are using proteinuria here as an overall marker of glomerular function.

Yet, the studies that you have shown us that examine the nature of the proteins in the urine are evidence that this is primarily a tubular problem. I wondered if you had explored the tubulopathy any further; that is, maybe some of this discordance is related to the fact that glomerular disease is not what is happening but tubulopathy is what is happening. Have you looked at other tubular functions such as potassium wasting, renal-tubular acidosis, things that could potentially be comorbid events here that the proteinuria could be marking and that we have not

really seen any data to effect.

DR. HUTCHINSON: Yes. We certainly did that.

[Slide.]

I can show you some data here regarding serum calcium, phosphorous and potassium in the patients with or without proteinuria on rosuvastatin 80 milligrams. You can see that there are really no differences in the level of serum creatinine, serum phosphorous, or serum potassium in patients with or without the proteinuria. So this seems to be an effect predominantly on tubular transport within the tubules. We are not getting a Fanconi's type of picture here with other abnormalities present as well.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: Just to clarify. To me, titrate means that you are adjusting the dose based on some indicator. In the changing from 80 milligrams to 40 milligrams, it seems to me that back-titrate is not the correct term, that you simply reduce the dose.

DR. HUTCHINSON: That's fair.

DR. WATTS: I want to explore what Dr. Woolf raised and what Dr. Follman raised and that

is the time course and is this resolution or is this variability? The slide you just showed indicated that 20 percent of patients in the 80-milligram group had proteinuria.

Table 15, and that analysis that you had--Table 15 of the FDA shows, by my calculations, there are probably 180 patients in the 40 and 80-milligram dose who had proteinuria and over 300 patients who had hematuria.

It seems to me you can look at the occurrence of these events by visit. That would be more convincing to me than what you see at the last visit represents a resolution rather than variability because my bet is, if this is sort of an erratic process, that what you would see at any visit is what you see at the last visit. It is only if you look over the totality of the exposure that you see when it shows up.

Whether or not this is a problem, a clinically meaningful problem, I don't know but I share Dr. Carpenter's concern that changes in serum creatinine may not be the best way to determine whether or not this is a clinical problem.

DR. HUTCHINSON: Can I please see the data that looks at our control pool and looks at the

evaluations of proteinuria at various time points, please. I will try to address your question using some of our control data.

[Slide.]

This slide is a little complicated. I was hoping to avoid this. But, having said that, what we are doing here is using the controlled-trial database. One of the issues within any time analysis is it can certainly be influenced if one of the groups has more visits, if the durations of therapy are longer.

We do know that for the 40-milligram dose group in our program, we started a large controlled trial and we had more visits and we were specifically trying to characterize some of the findings in our program using that trial. So, in general, there was a tendency for patients on 40 milligrams to have more visits and we know that, from our data, if you look at the placebo data, you can see proteinuria even on placebo.

But here, what we are looking at, is there are patients in our program that had shifts in urine protein to 2-plus or greater. This was our standard definition when we were analyzing our data. So that is why I am showing you this.

Numbers may change a little bit, if you are looking at slightly different levels of proteinuria but I think the trends are roughly the same. We are looking at Week 4, Week 6, Week 8 and Week 12. Notice, for some of the doses you see zeros, and that is because, in the trials that those patients were involved in, there just wasn't a visit at that time.

But here, at four weeks, in the rosuvastatin trials, we can see a signal up to 1.9 and 1.7 at the 40-milligram dose and, at the 80-milligram dose of rosuvastatin, it is 7.3, 8.4 percent at Week 6 ranging anywhere from 1 to 1.5. If we go out here to Week 8, what we are seeing is 1 percent, 1.2 percent. If we go out here to Week 12, we see 0.8 percent.

Now let's look at our comparators. At Week 4, we saw 0.3 percent here with simvastatin, 80 milligrams. If we go over to Week 6, we see a rate as high as 1.6 percent on placebo, 1 percent on atorvastatin 20. If we go out now to Week 8, we see 2 percent here in atorvastatin, 22 percent in simvastatin 20 and, if we go out here to Week 12, we see rates as high as 1.3 percent.

So, at the end of the day, the proteinuria

can be seen as early as Week 2 but it appears at various time points. There is no consistency with regard to, "I can tell you by Week 6 you are going to see all the proteinuria."

As you can see from this analysis, you can see rates as high as 2 percent in patients on the comparators where there is a reasonable number of patients on the comparators. So what we are seeing at 40 milligrams does not appear to be significantly different than what we are seeing with the comparators.

The fact that we did more measurements at 40 milligrams is probably contributing in part to the signal that you start to pick up at the 40-milligram dose group when you look at proteinuria at any time.

I hope that helps.

DR. WATTS: I would like to see that slide for a little bit longer.

DR. HUTCHINSON: Sure.

DR. WATTS: It could be made less complicated if, where you have no patients, you simply put an X and not a 0 because there are lot of 0s in the incidence column where there are 0 in the number-of-subjects column.

But, following the 40-milligram dose across, it looks like there is I don't know whether to call it an incidence or prevalence as it continues, because I don't know whether they are the same patients or new patients, but it is between 1 to 2 percent. That is not consistently seen for any of the other groups.

DR. HUTCHINSON: Part of the reason is because they haven't been measured at some of these weeks so you are not picking it up. But, at the end of the day, I think the important point here is that you can pick up proteinuria with the other statins. It is there. Whether or not that represents background or whether or not the statin is causing an effect, we don't know.

But, if you remember, we presented one of the cases in a South African patient who had a creatinine elevation along with proteinuria and hematuria and, in that particular patient, the rosuvastatin was stopped. The abnormalities went away. The patient was rechallenged with rosuvastatin. The abnormalities, the urinalysis abnormalities, came back. It was stopped. It went away.

The patient was then rechallenged with a

lower dose of rosuvastatin, 40 milligrams. And the urinalysis findings came back. So I think in some patients there is the potential that this effect can be seen.

But whether or not the numbers we are seeing here are background or actually a statin-related effect, especially for the other statins, it is difficult to know. I think, with rosuvastatin at 80 milligrams, we are certainly seeing a signal and there is potentially a signal at the 40-milligram dose.

But, once again, the key thing here is what happens in this patients with small amounts of proteinuria? Is the proteinuria at the end of the day resulting in any long-term or short-term detrimental effects on renal function? This program is a huge program and we are just not seeing it.

DR. BRAUNSTEIN: Dr. Kopp?

DR. KOPP: I have a couple of comments. Maybe I could start with this slide. One of the problems here is that it only twelve weeks of data. You could conclude, on the basis of what you said, that 80 milligrams of rosuvastatin is safe because there is no proteinuria at Week 8 and Week 12. I

think it simply points out the more valid issue is what happens after 48 weeks and 96 weeks.

DR. WATTS: There are no patients in the 80-milligram group at Week 8 and Week 12.

DR. KOPP: Oh; is that right? Sorry.

DR. HUTCHINSON: That's right. Exactly. There are no patients.

DR. WATTS: That is why I am saying it is an unnecessarily complicated slide because there are 0s where there are zero potential to have data.

DR. KOPP: Fair enough. Thank you for clarifying that. There are two issues I would like to make as comments. The first, one of the reasons for this variability is that dipstick proteinuria is not the ideal way to measure it. It may be the only practical way in a database of 12,000 patients but I think we need to recognize that urine concentration has a lot to do with whether the dipstick is positive or not.

In fact, if you want to be devil's advocate, you could say, with progressive tubulointerstitial disease, one of the first features of renal function to decline is the ability to concentrate. In a more dilute urine, you would tend not to see the proteinuria.

I am not necessarily sure that that is what is going on here, but I think some of this variability of proteinuria here, say, 4 percent of the time and then only present in 2 percent of the patients at the end of the study, may have to do with the limitations of dipstick proteinuria. So that is one comment.

The other comment is I think the model that I am thinking about, and I suspect some of the other people are, too, is this an agent that causes tubulopathy that may take a year or two to appear and cause proteinuria in a small fraction of patients, maybe 2 percent, maybe 4 percent, of patients which eventually will damage glomerular filtration by damaging the effect of glomeruli as well and lead to a rise in creatinine. But that may go on at three and four and five and six years.

I think we can't exclude that possibility. Many tubular toxins, in fact, take many years to cause their damage. Lithium would be a chronic class example. So that is two comments.

A couple of specific questions. Could you put Slide CS25 which was your data about protein-to-creatinine ration and albumin-to-creatinine ratio. The point here is

that glomerular proteinuria typically has more than 50 percent albumin; that is, more than 50 percent of the protein in the urine is albumin.

As you point out, 0.3 is less than 50 percent of 0.8. The probability is that that represents a mean of many patients. So, do you have the specific data what fraction of these roughly 300 patients had glomerular proteinuria? Was it, in fact, zero or was it a few?

DR. HUTCHINSON: It is not zero. Where we have SDS page information, it does show that the predominant pattern that you see is the SDS page, the tubular pattern.

If I can please see the data from-we looked at patients in our program that developed 1-plus or greater proteinuria to look at what types of patterns would be seen on gel electrophoresis.

I want the slides with the patients--

DR. KOPP: While we are looking for that, the page data are nice, but, in fact, you can get it from the 300 patients where you measured albumin, measured protein, measured creatinine and simply determine. That might be interesting to do.

DR. HUTCHINSON: I can show you some data in that regard, too, because we did so some of

these measurements as well. After I speak to these two slides, I think it would be worthwhile with regard to evaluation of our renal findings, we had several experts in the field of nephrology look at our data and advise us on how to appropriately evaluate our data in this large database.

We have Dr. Ed Lewis with us today. I think it would be appropriate for Dr. Lewis to make a couple of comments in this regard as well. But here we are looking at patients on the 80-milligram dose in our program. I think that this has--

[Slide.]

No; this is not the slide I would like to see. Can I please have the slide with the patients who went from 0 to 1-plus proteinuria. That has a couple of things reversed on it. Give me the data on the back-titration from 80 to 40 with the different types of proteins that were measured.

DR. BRAUNSTEIN: While they are looking for that, perhaps we can take the next question.

DR. KOPP: Can I ask a second question which changes, now, to the use of the drug in cyclosporine. Cyclosporine is also a proximal-tubule nephrotoxin. Do you have any comment about the occurrence of increased

proteinuria in patients who were on cyclosporine, rosuvastatin was added, and then the same question with regard to creatinine elevation. Again, cyclosporine elevates creatinine by hemodynamic mechanisms, later by fibrosis. Does rosuvastatin potentiate those effects?

DR. HUTCHINSON: The studies with cyclosporine were very short-term. Predominantly, they were pharmacokinetic studies and we did not pick up issues with regard to proteinuria or with creatinine elevations in those patients. But, in those studies, we were using low doses. I apologize for the time it took to get this slide. Hopefully we will find the other one in a second.

[Slide.]

These are patients in the substudy who had timed overnight urine collections, back-titration from 80 milligrams to 40 milligrams. These are the various proteins that were looked at along with n-acetal-glucose aminidase activity. What we see at the 80-milligram dose is that the proteins that were most prevalent in the urine were alpha-1 microglobulin, retinal-binding protein. We had lower levels of beta-2 microglobulin, albumin transferrin and IgG, but part of this was just due

to stability issues with beta-2 microglobulin.

What is critical here is, once we back-titrated patients to 40 milligrams, the largest changes that we were observing were in the alpha-1 microglobulin and retinal-binding protein groups. We saw smaller changes with regard to the other groups.

Have we found the other slide? We will have to try to find that over the break.

DR. KOPP: One other question, and I can yield the floor. How about glycosuria, a follow up on Dr. Carpenter's question. Any glycosuria in these patients?

DR. HUTCHINSON: No.

If the Chairman will allow, I can have Dr. Lewis come up and comment.

DR. BRAUNSTEIN: I think what we would like to do is to actually continue this discussion after the FDA's presentation. But I wanted to give Dr. Neylan an opportunity to ask his question.

DR. NEYLAN: Thank you, Mr. Chairman. Two question, both relating to renal effects. The first, as the sponsor has shown, I think the tubular-protein composition is certainly consistent--or, rather, the protein composition is

certainly consistent with a tubular site. I am not convinced yet that I understand whether this is a functional or more structural effect, though.

The reason I raise that is that this issue of hematuria arising in roughly the same incidence or prevalence as the proteinuria suggests the possibility that, indeed, there is a structural element here. As we know, a protein in the urine can be found in a variety of otherwise normal states. Hematuria is quite a bit less frequent.

The dipstick is certainly a convenient way of looking for the presence of hemoglobin but it is a surrogate for a microscopic examination of urine sediment. Urine sediment that shows a lot of cells and casts certainly raises the possibility of an activity or inflammatory state or even a state of increased turnover, be it tubular cells or glomerular cells.

So my question is when you received the approvable letter roughly a year ago and went back to do more detailed analysis of these renal findings, did you have opportunity to incorporate some evaluations of the microscopic elements of the urinalysis, look at sediment beyond just the dipstick and so could you share those with us?

DR. HUTCHINSON: I don't have a slide to show that, but we did have urine sediment evaluations on our patients with proteinuria and it did not show that these patients were having an active urine sediment.

DR. NEYLAN: How about in those patients that had hematuria by dipstick? Were you able to do any microscopic examinations of those urines?

DR. HUTCHINSON: We know it is red blood cells. Unfortunately, it is impossible now to go back at this stage and look at those previous urines simply because you need to look at fresh samples for the appearance of the red blood cells. This is something that we are doing now in our studies going forward but we don't have the samples to go back and evaluate them for red-blood-cell morphology.

DR. NEYLAN: My second question relates to cyclosporine. You mentioned that you were able to do a small study in heart-transplant recipients who were receiving cyclosporine as presumably one of the elements of their maintenance immunosuppressive regimen.

I am going to guess that, since most heart-transplant patients are not on cyclosporine

monotherapy, that this was a multidrug regimen. Were you able to tease out the potential impact or interaction of cyclosporine from any other elements in this regimen since there are well-known interactions with a variety of other immunosuppressants?

DR. HUTCHINSON: No; we have not done that.

DR. NEYLAN: I noticed the labeling of other statins does not necessarily get as specific as cyclosporine but mentions that, in the face of immunosuppressants, there can be warnings attached.

DR. HUTCHINSON: One thing that we did do was go back and look at our database and look at our hypertensive patients on various types of antihypertensive treatments because some antihypertensive treatments certainly can have effects on the tubules to see if patients having treatment with those antihypertensive agents increased the possibility of having proteinuria.

[Slide.]

So here we are looking at our highest proposed dose of rosuvastatin, the 40-milligram dose. We are looking at the association with various antihypertensive drugs of proteinuria, so

we are looking at ARBs, ace inhibitors, calcium channel blockers and diuretics.

As you can see, yes would mean that they were on the drug. No means not on the drug. This is the percentage with 2-plus or greater proteinuria, the percentage with 1-plus or greater proteinuria. As the data shows, there is no evidence that patients on these drugs would have an increased frequency of proteinuria.

So, once again, if there was some susceptibility there, we would expect to see an increased frequency and that is not happening.

DR. BRAUNSTEIN: Thank you.

We will now have the FDA's presentation. Following that, there will be some more questions from the committee, both to the FDA and to the sponsors.

DR. BRAUNSTEIN: Ms. Mele will give the efficacy presentation.

FDA Presentation

Efficacy

MS. MELE: Good morning.

[Slide.]

My name is Joy Mele. I am the FDA statistical reviewer for the Crestor application.

[Slide.]

I will be giving a short presentation on a few efficacy issues, so we are back to efficacy now. First, I will show the dose-response effect on LDL for rosuvastatin in three studies, Studies 8, 33 and 65. Then I will present a detailed comparison of rosuvastatin to atorvastatin using data from Studies 33 and 65. Lastly, I will describe the effect of rosuvastatin on HDL.

[Slide.]

To show the dose-response effect on LDL, I will presenting data from three dose-response studies in Type IIa and IIb patients, Studies 8, 33 and 65. You have already seen data today from Studies 8 and 65. 8 was combined with Study 23 in the sponsor's presentation. I will show you the data from these two studies and also from Study 33.

Recall, the doses in Study 8 were 1, 2.5, 5, 10, 20 and 40. In Study 33, dosing ranged from 5 milligrams to 80 and, in Study 5, an open-label study, dosing ranged from 10 milligrams up to 80 milligrams.

Studies 33 and 65 both included atorvastatin arms. The sample sizes in each treatment group varied considerably across these

studies with only about 15 in each group in Study 8 to about 40 in Study 33 and about 160 in each treatment group in Study 65. The baselines were similar across the studies at about 190 milligram per deciliter.

[Slide.]

This is a plot similar to what the sponsor has already shown you. Here is plotted the mean LDL percent change from baseline for the full dose range of rosuvastatin studied in the three trials I just described. I wanted to show here the consistency of the results across these individual studies.

Study 8 is shown in blue, Study 33 in green and Study 65 in red. The Y axis goes from 0 to 70 percent.

Looking at each dose, and taking into consideration the variability of these estimates, I would conclude that the responses are very similar across these studies. A dose response is evident in each study although, at the high end of the dose range, the 40 and 80-milligram doses, we see small differences of about 2 to 3 percent suggesting a leveling off of effect.

The benefit of doubling 20 milligrams to

40 is evident in Studies 8 and 33, and the sponsor showed this very nicely on a side earlier, but not so evident in Study 65, the very large trial. Note that the 5-milligram dose, which is plotted here, provides about two-thirds of the lowering seen for the 40-milligram dose, about 42 percent for 5 and 60 percent for 40. Dr. Lubas will make some additional comments about the 5-milligram dose in his presentation.

[Slide.]

From the data presented earlier by the sponsor, it was evident that the rosuvastatin is more potent than any other marketed statin on a milligram-per-milligram basis. Looking across the dose range, though, at what doses are rosuvastatin and atorvastatin comparable? Is twice the dose of atorvastatin needed to obtain comparable LDL lowering? How about four times the dose? I will address these questions in the next few slide slides by showing the treatment differences in the 96-percent confidence intervals.

[Slide.]

First let's look at a comparison of rosuvastatin versus two times atorvastatin. Using the data from 33 and 65, the two largest

dose-response studies in Type IIa and IIb patients, I have plotted the mean treatment difference in the 90-percent confidence interval for the difference. The values to the left of the 0 line favor rosuvastatin while the values to the right favor atorvastatin.

At the top of the graph is 5 milligrams versus atorvastatin 10. Then there is 10 versus 20, 20 versus 40 and 40 versus 80. Study 33 is plotted above Study 65 for each of the pair of estimates.

Focusing first on the blue boxes, the results look quite consistent, a difference of about 4 percent in favor of rosuvastatin is seen. The confidence intervals for Study 65 are tighter than for Study 33, as would be expected, given the large sample size, and the differences seen in Study 65 are statistically significant. This is the 0 line, and so you can see that these estimates do not overlap 0.

I just wanted to point out about the confidence intervals. These confidence intervals suggest that it is plausible that differences as small as 1 to 2 percent could be seen, not a clinically important difference. But they also

suggest that differences as large as 8 percent could be seen as well, which would be an important difference.

Since 40 is the highest proposed dose for rosuvastatin and 80 is the highest marketed dose for atorvastatin, I would like to examine this comparison further.

[Slide.]

Looking first to the graph on the left, these box plots show that 25th, 50th and 75th percentiles. The individual observations are plotted over the boxes. The overlap of the box plots show that some patients taking atorvastatin 80 can achieve LDL-lowering comparable to changes seen for 40 milligrams of rosuvastatin although the relationship of the boxes shows that a higher percentage of rosuvastatin patients will achieve significant decreases. The cumulative distribution plot to the right here, reiterates this point. The red line is rosuvastatin and the blue line is atorvastatin 80. The difference between the lines is illustrated by this vertical line at 60 percent.

About 23 percent of atorvastatin patients had a decrease of 60 percent or more while about

twice as many rosuvastatin patients had a decrease of 60 percent or more.

[Slide.]

What about four times the atorvastatin dose? Notice that all the confidence intervals overlap 0. Three estimates favor atorvastatin and two favor rosuvastatin, so there is no consistency across the estimates although the two estimates from Study 65--that would be these two estimates--are close to 0 and suggest comparability.

Now let's go on to HDL.

[Slide.]

There were four placebo-controlled, fixed-dose, phase-III, trials in the original Crestor application. The HDL results for these trials are listed here. The second column shows the baseline. The baseline in Studies 8, 23 and 24, all studies in Type IIa/IIb population, is about 50 milligrams per deciliter. In the Type IIb/IV population of Study 35, the baseline is about 35.

The underlying values indicate those changes significantly different from placebo. In general, the results are variable across the

studies in significance and also in magnitude of effect although some consistency is seen for the 10-milligram dose which would be this column here.

Note that the placebo subtracted estimates for the last two studies are both 8 percent. The lack of a dose effect is evident in both Studies 8 and 35 where higher doses show lower mean responses. You can see that here.

Now we will examine further the rosuvastatin dose response for HDL using the data from the large trial, Study 65.

[Slide.]

These box plots are of the HDL percent change from baseline for rosuvastatin in red and atorvastatin in blue. The grey boxes represent the confidence intervals about the medians. You can see a slight shift upwards of the confidence interval when going from 10 milligrams to 20 milligrams of rosuvastatin. This represents about a 2 to 3 percent more increase in HDL. Doses about 20 appear to afford no additional benefit so there is no clear dose-response relationship.

The results from Study 33, the other trial I showed you earlier, show a very similar pattern of research for rosuvastatin that is shown here.

The box plots for atorvastatin are clearly shifted downward. You can particularly see this if you focus on the 75th percentile at the top of the boxes. The atorvastatin response is more variable compared to the rosuvastatin response. If I showed you again the results from Study 33, you would see even more variability among the atorvastatin arms.

[Slide.]

So, in summary, rosuvastatin is marginally more effective than two times the dose of atorvastatin achieving about a 40 percent more lowering on LDL. It is clear that some patients may achieve comparable effects to rosuvastatin 40 with atorvastatin 80. The HDL effects are variable. There is no clear dose-response relationship with only a further increase of about 2 to 3 percent seen when doubling the dose from 10 to 20.

This lack of a dose response is consistent with what we see in the statin class although the atorvastatin results suggest more variability at the higher doses than what was seen for rosuvastatin.

Thank you.

DR. BRAUNSTEIN: Thank you.

MS. MELE: Dr. Lubas will speak next.

DR. BRAUNSTEIN: We will go on to the safety and dosing presentation by Dr. Lubas.

Safety and Dosing

DR. LUBAS: Good morning.

[Slide.]

My name is William Lubas. I am a medical officer in the Division of Endocrine and Metabolic Drug Products.

[Slide.]

I will be speaking to you today focusing on the issues of safety and dosing of rosuvastatin. In the first part of this talk, I will focus on safety.

[Slide.]

I will first address the issue of muscle toxicity associated with the use of statins. Statin-associated muscle toxicity has included CK elevations alone, myopathy, which is defined as CK elevations greater than ten times the upper limit of normal associated with muscle symptoms, and rhabdomyolysis, which is a clinical diagnosis which commonly refers to patients with very high CK elevations such as greater than 10,000 units per liter and/or patients requiring hospitalization for

IV hydration.

Since safe and effective statins with a low risk for the development of rhabdomyolysis are already currently available, any future statins which would be approved need to have a comparable or lower risk for this adverse event.

[Slide.]

This slide shows the incidence of CK elevations and myopathy seen with the use of statins. It summarizes the data from the clinical-development programs from Baycol, rosuvastatin, and for the pool of currently marketed statins. The incidence of myopathy includes all cases regardless of etiology.

While rosuvastatin doses of 40 milligrams and lower are within the range seen for other approved statins, there is a clear break at 80 milligrams. The two highest marketed doses of Baycol of 0.4 and 0.8 milligrams and the rosuvastatin dose of 80 milligrams had a similar frequency of CK elevations greater than ten times the upper limit of normal and myopathy, as you can see comparing here to here.

The frequency of CK elevations and myopathy is still higher for the 80-milligram dose

of rosuvastatin compared to all marketed statins even if one looks only at treatment-related cases as reported in the sponsor's presentation earlier this morning.

Baycol, at the highest dose, was found to cause severe myopathy and rhabdomyolysis in open-market use with a frequency not acceptable for the benefits of the drug with regard to LDL cholesterol lowering. Rosuvastatin, at 80 milligrams, is only marginally more effective than the 40-milligram dose and, relative to currently marketed statins, was associated with rhabdomyolysis in phase III of clinical development.

The expectation of greater risk in the less-structured and less-monitored setting of market use led to the conclusion of the unapprovability of this high dose.

[Slide.]

Now I will switch to the discussion of treatment-emergent renal adverse events now previously observed with statins which the sponsor has discussed in detail in their presentation and which they attribute to the decreased protein uptake by renal tubular cells due to

statin-mediated inhibition of HMG CoA-reductase in these cells.

[Slide.]

This slide shows the percentage of patients in the largest rosuvastatin safety data pool shown here, including all patients from all controlled and uncontrolled trials as well as real-time data with proteinuria by treatment group at any visit.

Proteinuria is defined as dipstick-positive urine of plus-plus or greater with at least one grade increase from baseline during the trial. The n here refers to the total number of patients in each group. The simvastatin, pravastatin and atorvastatin data came from controlled trials only while the rosuvastatin data included both controlled trials and open-label extensions and so had more patients as can be seen here. It also had longer duration of patient exposure.

The rosuvastatin data gave an appearance of an increase across the range of those who were studied, but there was a clearly visible transition at the 80-milligram dose where the peak incidence was 17 percent compared to all other statins which

had a frequency of less than 4 percent and were similar to the frequency of 3 percent seen with placebo.

This was true for patients on rosuvastatin in both the controlled and open-label extension trials which I will show more clearly in a subsequent slide. Patients who were back-titrated from the 80-milligram dose to 40 milligrams of rosuvastatin according to the sponsor, as discussed already earlier today, had a decrease in the frequency of proteinuria from about 8 percent at their last visit on 80 milligrams to about 2 percent at their first follow-up visit on 40 milligrams. This suggests the reversibility of the proteinuria seen here at 80 milligrams.

[Slide.]

This slide shows the percentage of patients with proteinuria at any visit summarized by the numbers on top of the bars subgrouped by dose and categorical increase in creatinine from baseline, as shown in the box. Proteinuria, again, refers to dipstick-positive urine of plus-plus or greater with at least one grade increase from baseline during the trial.

In this slide, the data are presented for

both the controlled trials, the lighter colors, and the open-label extension, the darker colors and labeled OLE. The serum-creatinine data is superimposed on the bars using tricolors subdivided by each group, as shown in the insert.

Red corresponds to an increase of greater than 30 percent from baseline. Green corresponds to an increase of between 20 and 30 percent from baseline and blue corresponds to patients with less than 20 percent increase from baseline.

So, for example, looking at the 80-milligram dose of rosuvastatin in the open-label extension trials, 17.2 percent of the patients had proteinuria at any visit. 11 percent of these patients also had an increase of less than 20 percent; that is, this would also include patients with creatinine decreases from baseline.

About 2 to 3 percent of these patients had an increase of 20 to 30 percent represented by the green bar and 3 to 4 percent had an increase of greater than 30 percent represented by the red bar.

I should just focus again that this data, in contrast to what the sponsor has presented, is data at any visit. The creatinine data is taken at the exact same time as the proteinuria data.

The higher incidence of proteinuria seen with the 80-milligram dose is also associated with higher incidences of serum-creatinine increases of both greater than 20 percent and greater than 30 percent from baseline. The greater-than-20-percent increase from baseline increase would correspond to the red and green bars, and the greater-than-30-percent increase from baseline would correspond to the red bars alone.

At doses below 40 milligrams, the frequency of proteinuria and creatinine increases from baseline is much lower. So it is hard to draw clear conclusions about these dose effects. The fact that the frequency of proteinuria appears to be higher in the open-label extensions compared to similar doses in the controlled trials suggests that the incidence of proteinuria increases over time. But this can be confounded by the irregular frequency of sampling of these trials.

[Slide.]

In addition to proteinuria, a subset of these patients had also had microscopic hematuria. This slide shows the percentage of patients with combined proteinuria and hematuria at any visit, subgrouped, again, by dose and categorical increase

in creatinine from baseline. Again, this is at any visit, not just at the last visit.

Here hematuria represents dipstick-positive urine of plus or greater with at least one grade increase from baseline. Over half of the patients with proteinuria at the 80-milligram dose shown in the previous slide also had hematuria shown here. So, for example, for the closed-label trials, 6.1 percent of the patients out of 11.8 in the previous slide and for the open-label extensions it was about 10.5 percent out of 17.2 percent of the patients.

This suggests that these two effects may be related. About 2 percent of the patients on 80 milligrams had a visit at which they had combined proteinuria, hematuria and an increase in creatinine of greater than 30 percent shown by the red boxes. This was true for both the open-label extension and the controlled trials at 80 milligrams and suggests an effect on renal function.

In contrast, only about a third or less of the cases of proteinuria at doses of 40 milligrams and lower, seen in the previous slide, also had hematuria in this slide. The incidence of

hematuria at these doses shown here is below 2 percent.

Again, at doses below 40 milligrams of rosuvastatin, the frequency of combined proteinuria and hematuria associated with the creatinine increases from baseline is much lower and so it is hard to draw any clear conclusions about dose effect.

While statin-mediated inhibition of protein uptake in renal tubular cells, described by the sponsor, may partially explain the proteinuria seen with rosuvastatin, it does not explain the hematuria or increase in serum creatinine seen primarily at the 80-milligram dose.

[Slide.]

These are cases that the sponsor has already addressed but I would like to focus on these a little more. In addition to the proteinuria and hematuria seen with rosuvastatin, there were two cases of acute renal failure of unclear etiology in patients receiving 80 milligrams of rosuvastatin for 15 to 31 days.

One of these patients had acute tubular necrosis noted on renal biopsy. There was also one case of chronic tubulo-interstitial nephritis after

18 months of therapy on 80 milligrams of atorvastatin. The renal biopsy was consistent with acute and chronic interstitial inflammatory changes and this patient had a positive rechallenge test with worsening proteinuria and hematuria with repeat exposure to rosuvastatin. This patient also had a positive rechallenge test, as mentioned before, to another less potent statin suggesting that this may, in reality, be due to a class effect.

These three cases, while serious, represent a small number of the patients out of the total of 12,000 exposed to rosuvastatin or the 1,500 exposed to the 80-milligram dose. It is important to note that all of these cases were seen at 80 milligrams and all patients improved after the drug was discontinued.

[Slide.]

There are still several unanswered questions about the renal findings. First, have the renal findings been adequately addressed? Clearly, most of the findings were at the 80-milligram dose which will not be approved. They were largely reversible on back titration from 80 to 40 milligrams and even patients with serious

adverse events recovered after the drug was stopped. But the effects at lower doses are less clearly understood.

Next, is some sort of monitoring needed, possibly at higher doses? Would urinalysis looking for proteinuria, hematuria and/or serum creatinine be useful for monitoring? Also, what further investigations are warranted to better understand the mechanism and the clinical course of these effects? Finally, is this a class effect of statins?

[Slide.]

In summary, the frequency of CK elevations and myopathy at doses of 40 milligrams or less is similar to that seen with other statins. The frequency of a 30 percent increase in serum creatinine above baseline in patients with proteinuria of plus-plus or greater is higher at doses of 80 milligrams compared to lower doses.

There is a suggestion that there also may be an increase with 40 milligrams but the overall incidence of proteinuria is so much lower at 40 that it is hard to draw conclusions from the current data. Clinical evidence suggests the renal findings may not be entirely explained by the OK

model of inhibition of protein uptake by renal tubular cells.

[Slide.]

The final issue the advisory committee will be asked to address is dosing. This slide presents mean LDL cholesterol data from two pooled trials, 8 and 23, in patients with Type IIa and IIb, primary hypercholesterolemia and mixed dyslipidemia with mean baseline LDL cholesterol levels in the range of 185 to 194.

The sponsor is proposing a start dose of 10 milligrams which would produce a mean LDL change of minus 50 percent. However, the 5-milligram dose, which is also available, is very effective at lowering LDL cholesterol and would produce mean reductions in LDL of minus 43 percent.

In one study of Type IIa and IIb patients, the 5-milligram dose resulted in 67 percent of the cohort reaching ATP-3 goals compared to 80 percent at the higher dose of 10 milligrams, a difference of only 14 percent more at the higher dose. It should be emphasized that, for many patients, the 5-milligram dose may be an adequate start dose based on baseline LDL levels and targets of therapy.

[Slide.]

This slide summarizes the recommended start dose for all currently marketed statins and the proposed start dose for rosuvastatin. The sponsor is currently proposing a start dose of 10 milligrams, 20 milligrams for patients with severe hypercholesterolemia with LDL cholesterol baseline levels above 190 milligrams per deciliter and 5 milligrams only for patients who are also receiving cyclosporine.

The 10-milligram proposed start dose for rosuvastatin would give mean LDL cholesterol-lowering greater than seen with all other currently approved statin start doses, yet the 5-milligram dose is also very effective.

[Slide.]

This slide describes the mean LDL-cholesterol reduction in statin-therapy clinical-event trials and it compares them to that seen with 5 milligrams of rosuvastatin. Although there are currently no clinical outcome data for rosuvastatin, it should be noted that the mean LDL reduction achieved with the 5-milligram dose exceeds those observed with other statins studied in large outcome trials.

This is true for both primary and secondary prevention trials. It is reasonable to assume, therefore, that, all else being equal, rosuvastatin, 5 milligrams, would be clinically effective as well as effective in treatment of LDL cholesterol to goal.

[Slide.]

This slide shows changes in AUC and Cmax with concomitant use of certain drugs or in special patient populations. Since no drug-drug interactions can increase serum rosuvastatin levels from two-to-seven-fold and specific patient populations may have two-to-four-fold increases in AUC over the average, labeling will need to address these situations shown in this slide.

The sponsor is currently proposing to limit the dose of rosuvastatin to 5 milligrams in patients taking cyclosporine to 10 milligrams in patients taking gemfibrozil and to 10 milligrams in patients with severe renal failure.

At present, the sponsor has not proposed alternative dosing for Asian Americans or patients with severe liver failure, even though the sponsor is currently seeking only a maximum dose of 20 milligrams in Japan. The sponsor does not feel the

need to cap the dose in the case of severe liver failure since they propose contraindicating the use of rosuvastatin in patients with active liver disease or unexplained persistent elevations of serum transaminases.

It is important that a wide dose range be available for these subgroups to permit optimal balancing of risk and benefit. Clearly, patients that have a decreased clearance for rosuvastatin will need to take lower doses of this highly potent statin.

[Slide.]

This slide shows steady-state rosuvastatin levels in asymptomatic patients receiving either 20, 40 or 80 milligrams of rosuvastatin in trials 8, 23, 33 and 35. These values are compared to samples taken 10 to 15 hours after the last dose of rosuvastatin from patients with rhabdomyolysis, myopathy or renal failure of unknown etiology shown in this last column.

These patients had all been taking the 80-milligram dose. There is no overlap in exposure among patients receiving 20 milligrams and those showing evidence of toxicity. There is a small overlap of less than 2 percent in exposure among

patients receiving the 40-milligram dose and those showing evidence of toxicity while about one-third of the patients on 80 milligrams had a steady-state plasma concentration above 50 nanograms per deciliter which was the lowest observed plasma concentration associated with toxicity in these patients.

These data suggest that drug-drug interactions or use in special populations with diminished metabolism or compromised clearance could result in increased serum rosuvastatin levels similar to those seen in patients with muscle and renal toxicity.

[Slide.]

In summary, as is seen with other statins, conditions that result in increased serum rosuvastatin levels above those normally seen with 40 milligrams may be associated with renal and muscle-related adverse events. Restrictive labeling will be necessary to limit dosing in patients at risk for higher serum rosuvastatin levels because of concomitant drug use or decreased drug clearance.

The sponsor is currently seeking to limit the maximum daily dose only in patients on

cyclosporine, gemfibrozil or in patients with severe renal failure as shown in this slide. We are asking if the sponsor's proposal to limit dosing is adequate and are there other conditions that may require limiting the maximum dose such as patients with Asian ethnicity.

[Slide.]

Also, in summary, the sponsor is proposing a start dose of 10 milligrams for patients with hypercholesterolemia and mixed dyslipidemia with baseline LDL less than 190. We are asking should the 5-milligram dose also be recommended as an alternate start dose. Unless we have clinical-outcome data, we cannot tell whether the greater LDL lowering obtained by starting all patients on 10 milligrams on rosuvastatin is of greater benefit than treating patients with lower doses of rosuvastatin or different, less-potent, statins to reach each patient's recommended LDL cholesterol goal.

While it is true, as the sponsor mentioned earlier this morning, that the safety profile of the 5 and 10-milligram doses of rosuvastatin in these trials was similar, clinical trials are always subject to limitations regarding conclusions

about absolute safety.

The possibility, therefore, always exists that higher doses of any drug are more likely to produce more adverse events especially when a much larger and more diverse population is exposed to the drug once it is available on the open market.

Thank you for your attention and we look forward to the advisory committee's discussion.

DR. BRAUNSTEIN: Thank you.

Question from the Committee

I will now open it up for further questions, both for the FDA representatives as well as to the sponsors. I would actually start with the sponsors since their pharmacokinetic studies is carried out in Japanese individuals in Japan showed an increase in serum levels, have you broken down the data as far as Japanese Americans are concerned? Is this an ethnic issue or is it an environmental issue?

DR. HUTCHINSON: Very good question. Certainly, after we saw the results of the our Japanese study conducted in Japan, we were interested in understanding whether or not the effects that we observed were due to either environmental or genetic factors.

There is only a small number of Japanese patients that have been exposed to our program outside of Japan so we can't draw any definitive conclusions from those patients. However, in response to the findings, what we have done is initiated a series of studies in order to understand this issue better.

We are conducting a study in Singapore, currently, that will be enrolling patients of Asian descent along with Caucasian patients. That will help determine whether or not we are seeing an environmental versus a genetic effect here.

But, in general, when we look at the data from the rosuvastatin programs in the Asians that have been exposed in the U.S., the frequency of adverse events, overall was similar to what we were seeing with the other comparator groups and there is no evidence that the Asian patients in our program were having an issue regarding tolerability to the drug.

If I may, Mr. Chairman, I would like to put up a slide to address Dr. Kopp's previous question. Do we have that proteinuria slide, please?

[Slide.]

You saw this data previously. It is just the headers were incorrect and I apologize for that. This is some data from the program regarding urinary protein electrophoresis patterns in patients with dipstick-positive proteinuria. Here we are looking at thirteen patients that have had pretreatment levels of proteinuria at 1-plus and the breakdown of the electrophoresis patterns in this patients.

Out of these patients, we saw eight with a normal pattern. None had a tubular pattern, two had a mix, and three with a glomerular pattern. With regard to patients on treatment who develop 1-plus proteinuria--there are 53 patients that we have in this cohort right now. We see fifteen of these patients had a normal pattern. Twenty-two of the patients developed a tubular pattern, nine a mixed and seven glomerular.

So the predominant finding on electrophoresis was a tubular pattern or a normal pattern

DR. BRAUNSTEIN: Thank you.

DR. LEVITSKY: Perhaps a point of information. I hadn't looked this up before I left. The other statins out there don't have any

suggestion that one should be checking for renal function or checking urinalyses, do they?

DR. BRAUNSTEIN: Dr. Orloff?

DR. ORLOFF: That is correct.

DR. BRAUNSTEIN: Dr. Kopp?

DR. KOPP: I had a question about monitoring for CPK, if we could leave renal for a minute. With regard to other statins, actually, is that presently monitored and do you have any proposals on monitoring your patients on rosuvastatin?

DR. HUTCHINSON: I will allow Dr. Orloff to answer the monitoring question for other statins or Dr. Lubas.

DR. ORLOFF: Unfortunately, I didn't bring my stack of statin labels with me but the basic principles of the instructions with regard to the potential for myopathy that are included in the labeling for the other statins hold that, while routine monitoring, per se, is not recommended, symptoms should be followed up and the finding of an abnormal CK requires follow up to assure spontaneous resolution or to guide reduction in dose or discontinuation of therapy if it is deemed potentially to be drug-related.

DR. KOPP: Is there a suggested cutoff above which, in terms of CPK-fold elevation, some change in therapy should be initiated?

DR. ORLOFF: Ten times the upper limit of normal is the action level that is recommended.

DR. BRAUNSTEIN: Dr. Neylan?

DR. NEYLAN: A question, again, about the muscle. There is clearly a spectrum of signs and symptoms associated with statin use. I have a specific question about a tolerability issue. Even in the absence of elevations of CK, myalgias are not infrequent with this class of drugs and can potentially be an obstacle to the patient and the prescriber.

I am wondering, is this a new entrant that looks to emerge in the market--I believe there are a total of seven now. Do you have any data relating to myalgia either overall frequency or intensity in comparison to some of the active controls you have had in your many trials?

DR. HUTCHINSON: Yes; we do have that data.

[Slide.]

Here is data from our controlled-trial pool. It is patient-reported adverse-event data

and we are looking at information on rosuvastatin in the comparators and placebo group in this pool.

What you see in general is that the frequency of any adverse event reported for rosuvastatin. This particular table contains information on the 80-milligram dose in addition to lower doses of rosuvastatin. With regard to any AE roughly similar to that reported with the comparators, we have, in general, a longer duration of therapy with rosuvastatin in this group and that needs to be taken into consideration.

But, with regard to myalgia, what we found is that the frequency of myalgia on placebo was 1.3 percent and we found a similar finding with rosuvastatin, 3.5 percent, atorva, 3.4, simva, 3.4 percent. Our pooled pravastatin gave us a 2.3 percent frequency.

DR. NEYLAN: You may be doing yourself some disadvantage by including the 80-milligram dose in this overall prevalence. Can you give us the breakdown minus the 80 milligram?

DR. HUTCHINSON: Yes. We can look at one of our other pools which is broken down by dose.

[Slide.]

This is a fixed-dose controlled pool. It

doesn't match up exactly with the other pool because, in this particular pool, what we are looking at is patients who initiated therapy at a specific dose in a fixed-dose trial or, in a titration trial, the data stops prior to titration of the patient. So whatever dose they start on prior to titration, that is the information that is included.

So, in general, what we found, looking at placebo and the doses of rosuvastatin from 5 to 80 milligrams in this pool was that the frequency of any adverse event reported was roughly similar.

If we now look at myalgia, we find the frequency on the placebo group was 1.4 percent and then we see that the frequency was relatively similar at doses from 5 to 40 but did increase at the 80-milligram dose.

DR. NEYLAN: Then, again, my question about whether you were able to compare it to the incidence of your active controls.

DR. HUTCHINSON: In this particular pool, we did not do that. But, in general, as you saw from the previous slide, the all-controlled slide, even including the 80-milligram dose, we don't see an issue with myalgia.

You did ask also the intensity. In the vast majority of the cases, the intensity of the myalgia was mild.

DR. NEYLAN: Okay.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: I had a question of clarification for Dr. Lubas. Slide 5, you looked at the percentage of patients with proteinuria at any visit and there was a clear, dramatic dose-response relationship within the rosuvastatin group and, as a whole, they had higher rates than the other groups.

I was wondering if that was based on common follow-up period for all of the groups or were rosuvastatin groups followed longer which would tend to make their rates larger?

DR. LUBAS: It is sort of a complicated question because it is more than just the length of time of exposure. It also has to do with the number of urine samples that were done. This data is combined for rosuvastatin for both controlled trials and for the open-label extensions.

Now, I could tell you that, in the controlled trials, it was more similar across all statins, that generally there were about two to

four samples, is what we are talking about in all these trials. Some of the open-label extensions had as many as nine or ten samples. But I don't think that is true for all of them and I could probably get you the data if you are interested.

So it is not just the length of exposure but it is also the number of samples at each of the doses that makes it very confusing. So it is hard do know exactly what the picture is in terms of whether the proteinuria is going away or being intermittent or what.

DR. FOLLMAN: My concern is whether it was sort of treating the different classes of statins fairly or not, was rosuvastatin being followed longer, did they have more visits where you were checking proteinuria than the other statins. It sounds like there is some difference between the classes of statins and this isn't really a fair shake to all the different statins in this picture.

DR. HUTCHINSON: I can give some information in that regard.

[Slide.]

This is our controlled-trial pool with rosuvastatin and the comparators, rosuvastatin 5 to 80, atorvastatin, 10 to 80, simvastatin 20 to 80,

and pravastatin 20 to 40. The number of patients in each of the group, mean days on dose; you can see it ranged up to 105, 106 days on rosuvastatin. You can see the range for the comparators. Patient years of treatment, much greater in the rosuvastatin group than in any of the comparators.

If you look at the number of follow-up visits, more in rosuvastatin than in the comparators. Now, if you look at the median number of follow-up visits to give some idea of did follow-up visits contribute to seeing a higher frequency of proteinuria here, you see, for rosuvastatin, 40 milligrams, as I had stated previously, there was more sampling performed on average.

Now, the only other group that also had three was the simvastatin, 80-milligram group. But, in general, for atorvastatin, there was a median of one follow-up visit and, at most, two for the other comparators.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: Yes. A question that arises from the efficacy data presented by Joy, and I believe it is her Slide 10, this is the HDL data. Although the mean and median increases in HDL with

statins is impressive and particularly for rosuvastatin, there are outliers that appeared on the slide that I don't think are visible on the handout that would suggest that there are actually some people who get quite significant reductions in their HDL. I wondered if we could get a better sense of that from the slide and, two, if there is any way to predict who these people are and if the drug was, for some reason, not effective in other parameters with this particular group.

MS. MELE: I will defer to the sponsor to answer that question.

DR. HUTCHINSON: I am going to ask Dr. Jim Blasetto who presented our efficacy data to please come and address the issues around HDL response, consistency of response.

DR. BLASETTO: Certainly, there is some variability in HDL raising with rosuvastatin that we saw. What we have looked at, as far as response to HDL raising that we have seen, we did see an increase in augmentation of effect in patients who had lower baseline HDLs, the slide that was shown by Dr. Rader in his presentation.

Also, we have looked at patients stratified by their baseline triglyceride and it

showed the patients with higher baseline triglycerides had more of an HDL-raising effect. So it appears that baseline lipid parameters clearly plays a role where we see a further increase in HDL.

[Slide.]

This is just to bring back what we had seen earlier. This is data from Trial 65, the STELLAR Trial, where we did look at response stratified by the cutpoint used by the ATP-3 guidelines as low HDL and higher HDL. We can see that, in the patients with low HDL, there was an augmentation of the HDL raising compared to lower HDL patients. We have seen that in other clinical trials where we have stratified the patients by HDL.

We have not particularly looked at the stratification of patients by other parameters for HDL effect. The effect has been really geared towards the baseline lipid parameters.

DR. CARPENTER: I just wondered if we could look at that slide again from the FDA presentation, I believe it was Slide 10.

[Slide.]

Thank you. I can barely see the blue

dots, but I believe that is what I was picking up. Some were down as low as 20 percent but, even within the confidence limits, some are down to 15 or so.

MS. MELE: That is 60 to 55.

DR. CARPENTER: That's right. I think it would be useful if the sponsor had any information about the people that have significant reductions in HDL and if, in fact, the ultimate outcome of therapy in some of these patients could be more detrimental than helpful.

MS. MELE: I just want to mention that this is LOCF data and that it is possible that those outliers could be patients who were not on therapy very long. But I wouldn't know the specifics. I didn't actually examine the outliers.

DR. BLASETTO: We have not looked specifically at individual--there are very few cases, actually. The outlier cases are very few and, in fact, if we look at the response seen with the atorvastatin doses, we see, also, outliers with reduced HTLC. As Joy said, in a last-observation-carried-forward response, I don't know what those individual patients represent, as to whether they were patients earlier on that could

have been carried forward without further therapy.

So that I can't specifically address those individual outliers. But, again, I think that we look at the response seen with the atorvastatin, we see, also, the outlier, several outliers, also.

DR. BRAUNSTEIN: Dr. Hennekens?

DR. HENNEKENS: I found the FDA presentation by Joy Mele and William Lubas to be very thoughtful and informative. Their presentations emphasized the effects of different doses of rosuvastatin from 5 to 80 milligrams on LDL, HDL, CK, myopathy, proteinuria and combined proteinuria and hematuria.

Based on these data, the agency raised the possibility of adopting a 5-milligram rather than a 10-milligram starting dose but made no comment on the possible desirability of 20 versus 40 milligrams as an upper limit of the dose.

I wondered if they would make a comment on that end of the range based on their analysis.

DR. LUBAS: I'm sorry; is the question about efficacy of 20 versus 40 or safety of 20 versus 40?

DR. HENNEKENS: I was thinking about the overall risk-benefit ratio because you presented

not only efficacy data but safety data on a wide range of parameters at the different doses but then made the conclusion about the starting dose possibly being 5 rather than 10 but made no comment at the other end of the spectrum about the use of 20 versus 40 as the upper limit.

DR. LUBAS: Right. The sponsor is only proposing the start dose of 20 for patients with LDL cholesterols of greater than 190 which would be a small percent of the population. I guess the sponsor could probably address this better, but they have a large number of patients that were started on 20 milligrams and it did have a good safety profile.

DR. HENNEKENS: I think, in part, the FDA would like to have the input of the committee concerning starting dose and maximum dose rather than to have the FDA, itself, take a stand at this point in time.

In terms of the tubular dysfunction that you see with the 40-milligram dose, have you looked at the interaction with possible other tubular toxins that patients may take; phenacetin, for instance, and other agents that can affect the tubules. Is there a potentiation of tubular

toxicity in those groups of patients because you certainly have a lot of patients on the drug at 40 milligrams?

DR. HUTCHINSON: I showed you a slide previously that did look at a number of antihypertensive agents and the potential effects of proteinuria. We can put that up one more time, but I don't have data on it.

DR. BRAUNSTEIN: But I think that had glomerular flow more. Wouldn't it be more of a glomerular issue rather than a tubular issue, the antihypertensives?

DR. HUTCHINSON: The diuretics, for example, were in the tubules so the expectation there is that there is the potential for synergy or some type of added effect on the tubule if a diuretic is given.

[Slide.]

When you look at our data in combination with the diuretic on this slide, we don't see, in patients with diuretics, that there is any potentiation of the proteinuria. We have also looked at patients in our program taking nonsteroidal antiinflammatory agents and we saw that patients on nonsteroidal antiinflammatory

agents, once again, there was no evidence of any renal dysfunction compared to patients not on nonsteroidal antiinflammatory agents. There was no evidence of a potentiation of proteinuria in patients on nonsteroidal antiinflammatory agents versus those not on those agents.

DR. BRAUNSTEIN: Thank you.

Dr. Temple, you had a question?

DR. TEMPLE: Dr. Lubas listed two patients with liver injury where he wasn't quite sure that there was a full explanation. You mentioned that they were rare, infrequent. I forget the word you used--patients who, in addition to transaminase elevation, had other problems. Can you say something about those or any of them, sort of pure hepatocellular cases or what are they?

DR. HUTCHINSON: There are two cases of patients, as Dr. Lubas mentioned in his briefing document, of patients that did have an increase in ALT associated with an increase in bilirubin. I can present the first case here.

[Slide.]

One was a 68-year-old Caucasian male, had seventeen weeks of rosuvastatin, 10-milligram treatment. This was a patient outside of the

current database so, presently, the 10-milligram database, if you include patients outside of our current database, is around 17,000 patients--so these are patients outside of that database--who was noted to have icterus and brown urine. When they evaluated the liver-function test in this patient, note that he did have an elevated ALT and AST with a mildly elevated bilirubin of 2.1

The patient was hospitalized, was on several medications. All were withdrawn. Liver histology showed normal parenchyma and he was discharged. Follow-up liver function one week after the event showed that everything went away.

DR. TEMPLE: Was the alkaline phosphatase slightly elevated in that one? I thought that is what I saw.

DR. HUTCHINSON: I don't recollect that. Somebody could look at the case, but I am not sure.

DR. TEMPLE: So the normal histology makes you think that it is not what you are worried about; right?

DR. HUTCHINSON: Right.

[Slide.]

The second patient that is in the briefing document is a 73-year-old Caucasian male subject

who, after 11 weeks of rosuvastatin, 10-milligram treatment, reported icterus, ALT and AST values, as you can see here, bilirubin, 11.8. However, this patient had a workup for hepatitis and the hepatitis showed hepatitis B surface-antigen negative but a positive IgM anti-hepatitis-B core antibody and hepatitis A IgG antibodies.

Also, in this patient, following discontinuation of rosuvastatin, the abnormalities resolved. But, in this particular patient, there is also a possibility that this could have been hepatitis related.

DR. TEMPLE: That one, for sure, had an elevated alkaline phosphatase of 300.

DR. HUTCHINSON: Right.

DR. TEMPLE: So that blurs it, too.

DR. BRAUNSTEIN: Dr. Kopp?

DR. KOPP: I would like to hear, if I could, from the nephrology consultant for the sponsor, Dr. Ed Lewis, who I know has thought a lot about this. Could you comment on your thoughts about mechanism, the possibility of a glomerular proteinuria and what your thoughts are about screening patients?

DR. LEWIS: This is my security blanket.

I am not sure it answers--

[Slide.]

Perhaps I could address some of the comments that you have made during the meeting, Dr. Kopp, and then you could tell me whether my comments are along the lines that you are looking for.

I think, first of all, just to remind everyone because tubular proteinuria is actually a rare phenomenon. So I don't want to indulge you about things that you already know, but I would point out that, in the normal person, albumin, a small amount, is filtered, as are low-molecular-weight proteins. 95 percent of these proteins are reabsorbed.

Microalbuminuria, which does vary, over the course of weeks and months, would be a slight increase in the permeability to albumin akin to the large permeability of albumin that occurs with glomerular proteinuria. Even though 95 percent of proteins are reabsorbed in glomerular disease, a great deal ends up in the urine primarily albumin and other proteins, but not low-molecular-weight proteins.

So what we are talking about here is

tubular proteinuria where the amount of normally filtered albumin and low-molecular-weight proteins are not normally reabsorbed. One of the questions that came up, for example, is could the fact that there are variations in urine protein excretion, since dipsticks are what was used--could that be due to a change in how dilute the urine is.

I think, in answer to that point, first of all, in terms of specific gravities that have been done during the study, there is no evidence that specific gravities went down. The serum sodiums were absolutely fine. There was no report of polyuria or polydypsia in the clinical reports so I think that this is not a dilution phenomenon.

Now, conceivably, and certainly it would be within the hypothesis that is being put forward about HMG-CoA-reductase alteration of tubular function, conceivably, there are variations in that from time to time and that could account for variations in tubular protein and certainly tubular proteinuria could go down well below what would be picked up with a dipstick, given those variations.

Can I have CO56?

[Slide.]

For me, the bottom line, actually, ends up

being when you look in all of the controlled and uncontrolled pool, leaving out the 80 milligrams which we are really not discussing today--if you look at the number with the creatinine increase of greater than 30 percent, you really don't have very much here.

When you look at the absolute changes in serum creatinine up to two years, even though there were greater than 30 percent increases in some of the studies in a few patients, these were almost entirely less than 0.5 milligrams per deciliter so that it is very difficult to predict what the future will bring. But I think that I would say that, on the basis of the data that I have seen longitudinally, these patients are not losing renal function.

Now, I would like to be able to tell you that I have seen forty renal biopsies and tell you what I saw in that. But I have seen one renal biopsy. This was from a patient who had proteinuria, hematuria and an elevation of serum creatinine of greater than 30 percent. It was perfectly normal. The histology was perfectly normal. The light microscopy fluorescence, there was little C3 in the arterioles and the EM was

normal. The only abnormality on that biopsy was that there was a fairly large arteriole in that biopsy which showed medial hyperplasia and I suspect that the hematocrit after the biopsy can't be related to the rosuvastatin therapy directly. I am sure it went down.

So that is the only thing that I can say, that there was no interstitial nephritis in that one case.

In terms of the hematuria, I think, and I am sure knowing your interests, I hope you will concur, that microscopic hematuria in a noninflammatory glomerular-nephritis situation is a mystery. It is seen actually very frequently, for example, after exercise. It is glomerular hematuria that occurs after exercise, just as an example, because, when you are exercising, actually your renal blood flow goes down so you can't say it is a hyperemic kidney losing blood in the urine.

Somehow, red cells do go through the glomerular capillary wall. It doesn't take very many, I think, to give a 2-plus dipstick but there is a transit and we have no way of knowing what that is about. The factors that are involved, be it an alteration in the glomerular epithelial cell,

that might allow slightly more of this than normal and so forth, I think it is not known.

Certainly, noninflammatory glomerular diseases like minimal-change nephrotic syndrome in children, a very large proportion of them have a very great increase in red-cell excretion. We know nothing about that. We have absolutely no understanding of the mechanism of how that happens and I think we can say the same is true here with rosuvastatin.

I think that all that we can really say is that the microscopic hematuria does track with this tubular proteinuria. It doesn't occur in an isolated sense. When the proteinuria goes away, the microscopic hematuria goes away. Whether that means that, given the common embryologic origin of glomerular epithelial cells and proximal tubular cells, and there is some change in function there, I think is a matter of significant speculation.

But I think that that is what we are left with. I don't know; has that answered all of your questions?

DR. KOPP: Yes. Just one final question with regard to screening. If you were putting a patient on rosuvastatin 40 milligrams with a plan

to leave them on it for the rest of their life, which somebody said earlier we hope to be a long time, would you want to screen annually with dipstick urinalysis.

DR. LEWIS: My feeling about that is, and I think it is particularly appropriate in this large number of patients who I think represent the people who are going to see this drug. They have cardiovascular risks. Half of them are hypertensive, probably using our more recent definitions of hypertension. I am sure well more than half of them are hypertensive. One out of six of them was diabetic and so forth.

They are on a host of drugs. My feeling about that is that the likelihood of getting not a spurious but a positive dipstick and a slight increase in the serum creatinine randomly is much higher than picking up something that is going to be related to rosuvastatin. I think that the physician will be left with, "Well, it is a positive dipstick, now what should I do?"

I think that since, especially in doses up to and including 40 milligrams, this appears to be a relatively unusual phenomenon. Since that is the case, I think that, both in a clinical sense and in

a cost-effective sense, it is not going to help greatly to routinely test the dipstick or test the serum creatinine.

I think that this population just has too many variations in those tests.

DR. BRAUNSTEIN: Thanks, Dr. Lewis.

Dr. Watts, you were next.

DR. WATTS: I want to go back to the efficacy issue and the HDL cholesterol. I am not sure that percentage change across the board is the right way to do it because some of the patients in the trial have reasonably good levels of HDL cholesterol.

Can you help me understand what happens to HDL cholesterol in patients whose levels are less than desirable who take the drug and what happens to patients whose levels are above desirable levels. In other words, a 30 percent decrease in somebody who has an HDL of 90 is not bad. Still, they are left with an HDL of 60 which is pretty good. But a reduction of 30 percent in somebody who starts at 30 is pretty meaningful.

DR. BLASETTO: I don't have individual specific data on patients on the baseline--you are talking about at baseline and then subsequently

achieved HDL. I think that the clearest answer on the HDL, who gets the most benefit, is really seen when we looked at the patients with low HDL and the response in the population and the patients with the HDLs above the 40 cutoff that showed less response.

The ones that would potentially benefit the most, the lower HDL patients, had the largest rise. As far as the mechanism of HDL effect there, Dr. Rader, who has done a lot of work on HDL metabolism and function, may want to comment on the rise we are seeing in the low HDL patients versus the higher HDL patients.

DR. RADER: I am actually not sure if you are referring to increases in HDL or decreases in HDL, kind of a follow up of that previous issue.

DR. WATTS: Changes in HDL.

DR. RADER: Changes in either direction.

DR. WATTS: The confidence intervals for all the doses suggested that there were some patients who had an increase and some patients who had a decrease. While, on average, the increase was 8 to 10 percent, the range suggested that some had significant decreases. There is also a partial artifact in looking at percent changes in a lower

group versus a higher group because the absolute change can be the same, yet the percent change looks greater in the lower group simply because you have started with a lower number.

DR. RADER: Let me just briefly address the decreases. In the clinical world, all of us always get asked by physicians, "Gee; I put a patient on a statin and their HDL dropped ten points, or fifteen points." It is a rare event. I think we have to emphasize that HDL measurement is the least reliable of all the lipid measurements. It requires a step involving precipitation. So there is technical variability and there is biological variability in HDL, actually quite a lot more than cholesterol in terms of issues that can happen on a day-to-day basis.

So I think these very small numbers of people who are having apparent drops in HDL, which, as Dr. Blasetto also said, is really not unique to this drug. It happened in the other statins, too, in the comparative trials. We have to interpret that very carefully.

I would say my bias, and Evan Stein might want to comment on this, too, as director of a major laboratory, is that these decreases in HDL in

these very small numbers of individuals is probably not a clinically substantial issue.

I think you are also raising the issue of percent increases in HDL and the clinical significance. I will be honest with you. As I sort of alluded to, we really don't know exactly how to interpret changes in HDL from a clinical standpoint. That is why I showed you that very simplistic 1 percent increase in HDL, 3 percent reduction in risk. That is integrated from lots of observational and clinical-trial data. It is our best guess right now.

But it is important that that is expressed as a percent, not as a milligram per deciliter because it does seem that, at least the data as far as we can tell, we are better addressing that with regard to percent changes than absolute changes. But I have to tell you, we have a lot more to learn about the HDL side of how it relates ultimately to risk.

DR. ORLOFF: Dr. Braunstein, I would like to make one clarification. The interpretation of those box plots that Dr. Mele showed, in fact the bars that go to the extremes of high and low are the range, are the full range, of values culled

from the database.

The 95 percent confidence interval around the median is actually the little grey box within, in the case of the rosuvastatin plot, the red box that represents, at the low end, 25th percentile, at the middle, 50th, and, at the top, 75th. So the 95 percent confidence interval around the median is actually very tight. In other words, there is a very small percentage of patients who fall into those outlier areas.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: I was curious to hear the sponsor talk about a trial that they are planning in 18,000 people where they are going to look at CVD events which was initiated a few months ago. I was wondering if they could describe that a little more and, in particular, how they will be monitoring kidney function in that study.

DR. HUTCHINSON: We would be happy to talk about those two trials. I am going to ask Dr. Jim Blasetto to mention it.

DR. BRAUNSTEIN: Maybe there could be very brief discussions because we do want to break for lunch. But I do want to finish this final round of questions.

DR. BLASETTO: The large trial that we have initiated in the United States and Canada is a trial around 15,000 patients who have elevated CRP levels and have baseline LDL levels below 130 so that these patients are non-CHD patients who have elevated CRP levels with LDLs below 130, who will be randomized in a double-blind fashion to rosuvastatin, 20 milligrams, or placebo and followed up for cardiovascular events. It is the Jupiter trial that we are doing. We will be following routine labs throughout the conduct of the trial as part of the follow up we will be doing.

DR. WATTS: How long will that study go on for?

DR. BLASETTO: We are anticipating that that trial will be at least--the patients will be at least three years in duration.

DR. BRAUNSTEIN: Thank you.

Dr. Neylan?

DR. NEYLAN: A quick question back to the hematuria. I was wondering if you had the opportunity to model some of the potential interactions of this very complicated patient population that you are dealing with, patients who

have variable risks for hematuria or proteinuria, diabetes, nonsteroidals, antiplatelet drugs and whether, either with univariate or multivariate modeling, any of these factors showed any relationship to the emergence of proteinuria or hematuria.

DR. HUTCHINSON: We haven't done any specific modeling. What we have done is some of the information which I showed you is to look at specific agents that were used by patients in our program to see if the use of those agents, in combination with rosuvastatin, resulted in any adverse effects on renal function. As I have shown you, there was no evidence of any adverse effect.

I can also, just to give people the scope of what we are doing with regard to the question of specific studies that will be ongoing, just show you types of studies that we are doing to understand this drug because I think it is important to know that we continue to study this drug and learn about it.

We have got studies on atherosclerosis regression. The METEOR is an IMT study using the 40-milligram dose. ASTEROID is an Ivus study, intravascular ultrasound, using the 40-milligram

dose. We have outcome studies ongoing, one with the GC group in Italy in heart failure, another heart-failure study known as CORONA, a study in patients with renal failure on dialysis called AURORA and Jim Blasetto just mentioned to you our JUPITER study which is in 15,000 patients with an elevated CRP.

So we will be continuing to evaluate this drug in ongoing work.

DR. BRAUNSTEIN: Dr. Woolf, you et the last question.

DR. WOOLF: I will try to make it brief. Continuing with the renal issue, if we are talking about a tubular abnormality, would one expect abnormalities in glucose transport? Would we see glycosuria, abnormalities in uric acid, excretion. Is it a different pathway or is it unique to the--the reabsorption unique to HMG CoA-reductase?

DR. HUTCHINSON: I am going to ask Dr. Lewis to please address that question.

DR. LEWIS: I think it is apparent in this particular situation that this is not a Fanconi's syndrome situation so that it is not a multiple renal-transport abnormality. What does appear--and I think that the in vitro cell-culture work may

shed some important light on this. It appears that this is a matter of protein transport, which is separate from the others and it probably somehow does involve melanic-acid metabolism.

There are known biochemical pathways that link melanic acid to the transport mechanism responsible for the endocytosis of proteins. So I think that that is what we really have here.

DR. BRAUNSTEIN: Thank you.

We will break now for lunch and reconvene at 1:30 with the open public session.

Thank you.

[Whereupon, at 12:48 p.m., the proceedings were recessed to be resumed at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:30 p.m.]

DR. BRAUNSTEIN: We will now go into the open public session. We have had one request from Dr. Sidney Wolfe, Director of the Public Citizens Health Research Group is going to make a very brief presentation.

Open Public Hearing

DR. WOLFE: I think I was told I have ten minutes. If that is brief, that is fine. Thank you. I have a handout which I think has been distributed to all the members on the committee. I will just go through it as quickly as possible.

It starts out by looking at the data on Baycol, the reason being that, like this drug, rosuvastatin, Baycol also caused rhabdomyolysis. In this first chart, what we have done is looked for each dose that Baycol was used at, all of the adverse-reaction reports that were filed with the FDA as the denominator. The numerator is the number of those cases, or proportion of those cases, that were rhabdomyolysis.

What you can see, and it is also depicted in the graph below, is that as you go from 0.1 milligrams--remember, Baycol was 0.1 milligrams as

opposed to 10--up to 8, you go from 3.5 percent of all the adverse reactions being rhabdo up to 54 percent.

Since this is in clinical use, not a Phase III trial--it is clinical use--these are all people who took the drug long enough to have a problem, although the latency period for Baycol is shorter than for rosuvastatin or for the other statins.

The next chart points out something that was briefly alluded to in the FDA's documents but not discussed this morning at all which is that, if you look at the average duration of treatment of people in the trials as a function of dose, what you see is that, at 40 milligrams, for instance--and this is derived from looking at patient years divided by the number of patients--at 40 milligrams, you see that the average duration was about a quarter as long, 117 days, as opposed to 453 days at the 80-milligram dose.

This is important because, for the cases of rhabdomyolysis that the FDA has described and the company has described, the average duration of time was 280 days. So, not surprisingly, those are all cases at 80 milligrams. There was one, as you remember, at 10 milligrams. But, not surprisingly,

for the dose that, in fact, had a much longer duration, it was much more likely, for that reason amongst others, that you would see cases of rhabdomyolysis.

For the 40-milligram dose, where people are taking it for a quarter as long, it is less than surprising that there were no cases of rhabdomyolysis or that there wasn't a more regular steeped increase with dose as we had seen with Baycol.

Again, these are just taken from the data that the FDA had in its presentation, just transmitted into bar-graph form, vertical bar-graph form as opposed to the horizontal that the FDA did. But here what you see is that, for the creatin-kinase elevations of 10 or greater, it really kicked off mightily from 40 milligrams up to 80. It was 0.4 percent of the patients at 40 milligrams at 1.9 percent at 80. Again, I think that this is certainly consistent with the fact that so few of the patients in the 40 and 20 milligram dose had a long enough duration. The suggestion here was, in order to more accurately assess the incidence of CK elevations at each dose, you need to have duration-adjusted data for CK elevations.

For example, what was the incidence of CK of 10 or greater in those patients who had longer exposures to 40 or 20-milligram doses whereas 56.8 percent of the people getting 80 milligrams or rosuvastatin were exposed to longer than 48 weeks, only 6.5 percent of those getting 40 and 8.4 percent of those getting the 20-milligram dose were exposed for more than 48 weeks.

As I just alluded to before, I think that this is certainly a plausible hypothesis why you don't see the gradual dose-response increase that was there at least in the way in which we analyzed it with Baycol.

I just have inserted here directly from the FDA's presentation some of the further--most hospitalizations were preceded--this is rhabdo--by a 3 to 28-day prodrome suggesting a viral illness with subsequent dehydration as a possible precipitating event.

We are just finishing for publication an analysis of the Baycol data versus the other cases of rhabdomyolysis. The latency period is much shorter for Baycol than for all the others. The latency period here is pretty much the same as for the others. The mortality, if the denominator or

cases of rhabdo in the numerator or deaths is much lower for Baycol, and I suspect that may have to do with the fact that the sooner after starting the therapy it comes, the more likely someone may link it. I remember talking to someone whose father died--hey thought he had the flu--after he started Baycol at age 81 and they kept him on the drug in the hospital and he died of acute renal failure a couple of weeks later.

So these longer latency periods may make it trickier to pick up things, particularly when you are not in a trial.

On the renal damage, I think that the combination of proteinuria and hematuria has been described as a structural thing not just some functional kind of problem. The chart here--again, this is taken from FDA's presentation--increased proteinuria with increased dose. These were people with three or more increased grades in proteinuria and it goes from 0 at 5 milligrams up to 5.4 percent at 80 milligrams.

The point that I just wanted to make briefly here is that, whereas it looks like there is a very long latency period for the rhabdomyolysis, it appears that, in a much shorter

period of time, at least the early evidence of renal damage, the hematuria and proteinuria, can occur and, therefore, the problem with not seeing cases at 20 and 40 of the rhabdo or even the CKs seem to less of a "problem" here. There were increases starting at 10, stepwise, up to 20, 40 and up to 80 milligrams.

The next chart is just looking at atorvastatin from, again, the data that were in the report showing that patients with increased proteinuria and hematuria, it was pretty flat. There were no data available at 5 milligrams, at 0.6, 0.3, 0.4 and 10, 20 and 40 milligrams and none at 80 as opposed to the next chart which is showing a very stepwise increase in proteinuria and hematuria with increased rosuvastatin doses.

I just want to quote, because I think it sort of summarizes the concerns that I and, I think, many other people have about where does this hematuria and proteinuria go, and there were these three cases. I am just quoting from what was written. It was described very briefly this morning. These three cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern which is similar to

the renal disease seen with rosuvastatin in these clinical trials.

There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis. All cases occurred at 80-milligram dose which was also associated with the greatest number of patients with abnormal renal findings, the hematuria and proteinuria.

Proteinuria and hematuria could potentially be managed. I was concerned to hear the response to the question about should you be screening for this. I think that the answer that you don't screen because it might be confusing is the wrong answer. I am sure that the company is screening, or should be screening, not just with dipsticks but, hopefully, even though they didn't do them before, getting some urine sediments.

"Proteinuria and hematuria could be potentially managed with regular urinalysis screening." This is the quote from the FDA's document. "However, they are the signals for potential progression to renal failure in a small number of patients. This may represent an unacceptable risk since currently approved statins do not have similar renal effects."

Then, just in summary, well within the ten minutes, I think, we strongly oppose the approval of rosuvastatin because of its unique renal toxicity. We are also seriously concerned because of the seven cases of rhabdomyolysis that were common enough to have shown up in clinical trials. Unlike preapproval studies with all previously approved statins including cerivastatin in which no cases of rhabdomyolysis showed up prior to approval.

The fact that so few patients on the 20 or 40-milligram doses took the drug for a sufficient period of time to have had a chance to develop rhabdomyolysis seems to have imparted a false sense of security about the safety of these doses concerning muscle toxicity. The increased ability of research to lower LDL cholesterol is most clearly seen at the 20, 40 and 80-milligram doses, although, as pointed out, there is some increase at 10 and 5.

If this drug is approved, it is highly likely it will have to be removed from the market after enough further damage to patients occurs.

If there is a minute or two, I would be glad to try and answer any questions.

DR. BRAUNSTEIN: Thank you.

Does the committee have any questions for Dr. Wolfe?

DR. KOPP: On Page 4, the y-axis is greater than three grades, so that would mean going from--this is the proteinuria data--going from negative, greater than equal to three grades, to going to only those patients who are negative at the beginning, going to trace 1-plus, 2-plus?

DR. WOLFE: The greater or equal to three grades is taken directly from, I guess it is Table 15 in the FDA presentation. This is what they said. It had to have increased the degree, as measured by dipstick, the proteinuria had to have improved, increased, rather, at least three grades.

DR. HENNEKENS: Dr. Wolfe, as always, I find your comments thoughtful and provocative. One of the issues that you have gotten your hands nicely around, in the issue about duration leading to rhabdo, is the dose of the drug. But the other idiosyncratic issue with gemfibrozil that is not mentioned your analysis.

So I wondered if, in addition to the dose issue, you have looked at the duration of the combination therapy with gemfibrozil to see if that

long duration is confounded, if you will, by the use of gemfibrozil which had the idiosyncratic deleterious reaction with cerivastatin.

DR. WOLFE: We looked for that in this dataset that we have analyzed, the Baycol and all the other statins, and there was some interaction there. I can't remember the numbers now. We analyzed this a few months ago. This is not this drug. It is the other ones. I don't know exactly--you saw, in one of the slides this morning that, in combination with gemfibrozil, I think the area under the curve went up twofold. I think that was the number.

So your question is a good one. It sort of has the effect of shifting the dose and it may make at least a small subset of 40-milligram people look like they are getting aid. But, again, the duration is a problem. I was astounded when I did these calculations based on the data in the FDA that there is a four-fold difference in the duration between the 40 and 80, and the average is so far down there below what the average period of onset of rhabdo is in the 80, that I don't think that we have any kind of answers to the question of how much CK elevations, how much rhabdo, there are,

particularly in the 20 and 40.

It is interesting that, at the lower dose, at the 5 and 10, there is longer duration. But the worry is less there, I think, than at the higher dose, the higher doses being 10 and 20. I would be very interested in the discussion--I am going to have to leave--as to what you think the maximum dose should be, because this starts getting into an area that we don't have answers for in terms of the paucity of long-term data in those two groups.

DR. HENNEKENS: That leads me to my second and last query which is, if one looks at LDL, HDL, CK, myopathy, proteinuria and combined proteinuria and hematuria, and one looks at the range of doses, the 5 to 20-milligram doses, one could say are at least comparable or even more favorable than the five marketed statins.

Yet, you came to the conclusion that it should not be approved. So I was curious to your thinking on looking at, if one looks at that subset of patients with regard to the total--

DR. WOLFE: Let's go back to the suggestion that was made, or at least that put forward for discussion, that 5 milligrams should be the starting dose. At 5 milligrams, the

differences between the statins, particularly if you go with this doubling effect, are not that significant. You have other statins that do not have, and I think everyone agreed on that. There is no evidence of renal toxicity which is what this is in any of the other statins. Now that Baycol is off the market, none of the other ones are even close in terms of the likelihood of rhabdomyolysis.

So you have two strikes against this drug in terms of safety and if, by doubling up on the dose of atorvastatin or whatever one you choose, atorvastatin is the one that was looked at in these studies, if you can achieve the same kind of LDL lowering at 5 or 10 milligrams, why approve the drug which has negative risks compared with the other and the benefit is achievable by just a higher dose of other statins. That is really the basis for what our conclusion was.

DR. BRAUNSTEIN: Thank you, Dr. Wolfe.

The sponsor is going to address two issues explicitly that were asked by the FDA and the committee. One concerns 20 milligrams versus 40 milligrams being the top recommended doses and what the rationale for the 40-milligram dose would be. The second concerns a starting dose of 5 milligrams

versus 10 milligrams and what the rationale for going to 10 milligrams is.

Sponsor Comments

DR. HUTCHINSON: If I may, I could also shed some light regarding do we have sufficient exposures at the 40-milligram dose to justify its use.

[Slide.]

We have looked very carefully in the myopathy and rhabdomyolysis cases in our program. What we have found is that, in general, the hazard for these events was relatively constant with rhabdomyolysis cases just dispersed amongst the myopathy cases.

Now, if we look at our data that I showed you earlier with regard to continuous exposure to rosuvastatin at the various doses, the data in this column is extremely important data with regard to whether or not there is a long-term effect with regard to rosuvastatin at the 40-milligram dose on myopathy and rhabdomyolysis.

We have over 1100 patients exposed for greater than 48 weeks and, as you can see, close to 900 patients exposed for over two years. There is no evidence in this group that we are seeing an

increased frequency of rhabdomyolysis or even any additional rhabdomyolysis cases or myopathy cases.

So, in general, we have a large database of patients with long duration of therapy to high doses of rosuvastatin without any evidence that, at the 40-milligram dose, we are seeing an increased frequency of rhabdomyolysis or myopathy at later durations of therapy.

Now, with regard to two key questions that are going to be addressed by the committee, those questions are regarding the top dose of rosuvastatin. We have shown you some key efficacy data regarding the importance of the 40-milligram dose. I would like to have Dr. Christie Ballantyne and Dr. Evan Stein just briefly discuss the importance of having that 40-milligram dose. Dr. Thomas Pearson is going to come up and talk about the 5 versus the 10-milligram starting dose of rosuvastatin for the general population.

Dr. Ballantyne?

DR. BALLANTYNE: Thank you. Christie Ballantyne at Baylor College of Medicine. If I could have CO63, please.

[Slide.]

As someone who is a cardiologist by

training and used to looking at the risks and benefits of treating patients with cardiovascular disease. It is sometimes interesting to see the inconsistencies in regards to what we have traditionally done in treatment atherosclerosis. We routinely do bypass surgery and angioplasty which do not reduce mortality and accept extraordinarily high event rates of complications with this.

I hear great hesitancy towards treating lipids. It has evolved. When I started in 1988, people said, "You shouldn't do this at all. It is dangerous." What I think is we have evolved tremendously. You saw the data from the clinical trials earlier today but I would point out that don't forget in the 4S study, the five-year event rate in the treated patients was 20 percent or MI or death.

This is a very high--it is a disease that causes tremendous morbidity and mortality. It is a leading cause of death in our society. As a clinician, what I am faced with is, on a regular basis, seeing patients who have either very severe atherosclerosis that we are treating aggressively, sometimes familial hypercholesterolemia or combined

hyperlipidemia, but very many patients who are difficult to treat.

I routinely have been making the decision of do I titrate 40 to 80 milligrams of simvastatin? Do I go from 40 to 80 milligrams of atorvastatin. I have done this on a routine basis based upon the evidence that better reductions in LDL cholesterol lead to greater event reductions.

Now, I do that despite the fact that there is an increase in transaminase elevations as you go from atorvastatin 40 to 80. Some of these also include elevations of alkaline phosphatase. The mechanism is not well understood, but it does not seem to be a major problem. If it is discontinued, it resolves.

With simvastatin, there is an increase also in transaminases. With both agents, there is an increase in the risk for myopathy with that. So what I see is another opportunity to provide better reductions in LDL cholesterol for my patients with actually what appears to be, in comparative studies, a lower risk for the ALTs, certainly no increase in risk in terms of the CK elevations.

We do have this issue of proteinuria. But I think if we look at this once again in terms of

numerically, it is small, a low percentage and if we look at what happened with creatinine, elevations that were 30 percent that persisted, which would be 0 across the board, that, if one weighs the risks and benefits for this in regards to the pain, suffering and death from cardiovascular disease, in my opinion, it is very favorable with this for having 40-milligram dosage which we can use to aggressively treat patients to try to reduce cardiovascular morbidity and mortality.

I would like to turn it over to Dr. Stein.

DR. STEIN: Thank you and good afternoon. I am Evan Stein from the Cincinnati area. My career has been spent in treating hyperlipidemia. Specifically, my interests are in those groups of patients with inherited high cholesterol.

We heard earlier about familial hypercholesterolemia and a number of the studies that were done and I am going to turn to this population.

If we can have the first slide, CO40.

[Slide.]

Just to remind you that this is a common genetic disorder that, although heterozygous

familiar hypercholesterolemia is not that well recognized, there are over a half a million patients in the United States and these patients have a monogenic disorder which, from birth, gives them very high LDL cholesterol levels, results in very early coronary disease. Average age of onset of coronary disease is 40 to 50 years of age in men and 50 to 60 years in women and it is very difficult to treat.

In addition to about these half million, there are probably another half million patients who have severe polygenic hypercholesterolemia. So there is a population of about a million patients out there who have high risk for coronary disease due to very high LDL levels.

[Slide.]

Just to show you--this is the largest database. This is a database from Utah in something called the MedPed Registry which is for familial hypercholesterolemia. This is over 40,000 patients in this database. You can see here is the coronary-artery disease risk or incidence in women who don't have familial hypercholesterolemia. The blue is men who don't have familial hypercholesterolemia.

This is women. You can see by about age 60, these women exceed the incidence of even an 80 or 90-year-old woman and exceed generally all the way along that of men. By age 50, this far exceeds that of an 80-year-old man. This includes patients who are currently treated. If you look at the very high, by age 65 or 70, nearly eight out of ten have coronary disease.

If I can have 42, please.

[Slide.]

When we look at the effects of the one study which was shown earlier which was Study 30, a large study, over 600 patients with familial hypercholesterolemia, 432 on rosuvastatin, nearly 200 on atorvastatin, which is the current standard for monotherapy for these patients.

You can see here that, at 20 milligrams, we got a 47 percent reduction in LDL and, at 40 milligrams, a 54 percent reduction. Here is the atorvastatin at its maximum dose of 80 milligrams.

Next?

[Slide.]

Now, that doesn't sound like very much in terms of 7 percent. Now, remember whenever we are looking at this percentage, we are going back to

their baseline LDL levels. So, if we go back to the baseline LDL levels which were 290 for this population, very high levels, you can see that the 47 percent reduction resulted in a new level now of 154 milligrams. That is a 47 percent reduction.

When you went to 40 milligrams, although this difference is only 7 percent, because it is 7 percent of a base, we don't actually do that in practice. We give somebody 20 milligrams and then we look at their baseline and we give them another dose or we add another drug.

When you do that, the mean here is 133 which is actually another 14 percent decrease in LDL cholesterol, very similar to what we would get by adding a second drug to any 20 milligrams of the existing drug.

If we can go to the next slide.

[Slide.]

What this translates into, even though it is only a 7 percent difference, it translates into a big difference in terms of these severe patients getting to an LDL goal of less than 100. So it is an average of around about 21 milligrams per deciliter reduction. It takes you from 6.5 percent of these patients to nearly one in six now getting

to LDL control.

If one compares this to the standard effect of monotherapy, atorvastatin 80 milligrams, you can see less than 5 percent. One could say, we could achieve this by adding a second drug.

If we can go to No. 46.

[Slide.]

If we now look at a similar study, and I think that Dr. Rader mentioned this earlier, this is also a study of over 600 familial hypercholesterolemic and severe hypercholesterolemia patients whose LDL goals were also less than 100. Here the design was that everybody started at 10 milligrams of atorvastatin, had an LDL of above 130 and was then dose-titrated depending on response aiming to get LDL below 100.

This is the FH group which makes it very similar to this population. You can see that going up to 80 milligrams of atorvastatin resulted in remarkably similar number of patients, less than one in twenty, achieving the LDL goal whereas this was the combination of atorvastatin, 40 milligrams, plus ezetimibe 10, achieved roughly the same amount of patients getting to goal.

Now, while this is a big step for FH

patients, and I have over 400 patients in my clinic on this drug, the majority of which are FH patients, this was a big step for them to be able to go to monotherapy because, in the past, they had been on two or even three drugs including high-dose niacin which is another potential adverse risk factor when added to high-dose statins.

You can see that, with monotherapy, we now have made at least progress. Not having this 40-milligram dose available for the FH patients is going to basically leave us at the starting point, at this endpoint, rather than using this as a new potential starting point for these patients where we can perhaps get, with the addition of a second or third drug, maybe half of them onto treatment that would provide them with optimal therapy.

Thank you.

DR. BRAUNSTEIN: Now we are going to discuss the 5 versus 10 starting dose.

DR. PEARSON: Good afternoon. I am Tom Pearson from the University of Rochester where I direct a preventive cardiology clinic. I am a cardiovascular epidemiologist by training and interested in really population trends in lipids and particularly in the extent to which goals are

attained according to the current guidelines.

I would like to address this 5-to-10-milligram issue on that basis and maybe begin by saying, and maybe taking a chapter out of Dr. Hennekens' research, is that if you have a drug with flat safety and efficacy across the dose range, such as aspirin, you are likely to take the lower dose to get the job done.

What I am going to suggest is you don't really have flat efficacy even across the 5-to-10 range but we are going to have to go into epidemiologic and modeling data to do that because there is never probably going to be a clinical trial comparing 5 milligrams and 10 milligrams.

So let's look and see what we could expect in terms of a difference in benefits between 5 and 10 milligrams.

[Slide.]

These are data from a metaanalysis of lipid-lowering trials which basically gets to the point of there is thought to be a graded response. The lower the LDL, the lower the event rate, even at these lower percent reduction areas that we have, even here, in terms of the middle ranges.

[Slide.]

This has led to this rule that we use, 1 percent reduction in LDL can confer a 1 percent reduction in coronary-disease risk. Similar kinds of analyses have led to a different equation with HDL and that is, for every 1 percent increase in HDL, we have a 3 percent reduction in coronary risk.

So let's look at what we might surmise in terms of the benefits we get between 5 and 10 milligrams. Here you have the LDL, about a 6 percent reduction, which should confer another 6 percent reduction and risk and perhaps about a 1.3 percent rise in HDL across and the dose-response--there is a dose response, apparently, to HDL at these lower doses of rosuvastatin. This should give an additional 4 percent.

So the point here is that I think what we are talking about--at least in lieu of randomized head-to-head trials, you are talking about a 10 percent risk differential between the 5 and the 10 percent. The importance of this, as a population scientist, is that this is the starting dose. This is where the belly of the population curve is going to be treated. These are where most of the

patients are going to be treated at in terms of current practice patterns in terms of statin therapy.

Therefore, this spread over a large number of individuals, I think would be a very meaningful effect.

[Slide.]

The second point I wanted to make is more of a medical sociologic one and that is the extent to which people are at goal when they start a certain dose. This is the percent attaining ATP-2 guidelines with the starting dose. I think you can see, between atorvastatin at 10 milligrams and rosuvastatin at 10 milligrams dose, you have quite a large difference in the percent of individuals who will actually be at goal.

I want to have my primary-care providers get this amount of efficacy at the starting dose. I will remind you that the NHANES data from 1999 to 2000 currently shows that only 47 percent of hypercholesterolemic patients are basically controlled. This is a representative sample of the U.S. and so would be even worse. If we had a more efficacious starting dose of 10 milligrams, we would get the vast majority of those individuals at

goal.

So I think, on a population basis, it is important that we have a 10-milligram versus 5-milligram dose because I believe there is a change in efficacy and there is a reluctance of primary-care providers, in particular, to accelerate doses above that and get to goal.

Thank you very much.

DR. BRAUNSTEIN: We will move into Dr. Orloff's charge to the committee.

Charge to the Committee

DR. ORLOFF: I hope I am ready for that. First, let me say that the discussion has been very helpful. I just want to remind the committee that this is a confusing, and to some extent, frustrating process for you all. I understand. We don't expect you always to be able to give us absolute answers. So don't away discouraged if you sometimes cannot produce them.

The question of risk versus benefit is always the most difficult one we grapple with because, by definition, it is an impossible calculation. Benefit is apples and risk is oranges. Last I checked, you can't subtract one from the other.

I guess, by my way of thinking, actually referring to just some of the recent remarks made, there are a couple of points that come to mind. One is that I do think that there is a compelling argument in the issue of tolerance of risk and the example of Dr. Ballantyne, surgical versus medical intervention for cardiovascular disease. I do believe that we all need to keep that in mind.

The other thing is, regardless of exactly what calculations you want to go with and what estimates of incremental benefit you are going to believe or expect, I think there is compelling evidence that exists today as well as much more to come--of course, what that evidence is, we can't necessarily predict--that lower LDL is better.

So I think it is reasonable to assume, on the benefits side, that, on balance, having an improved or an ability to lower LDL additionally beyond what can be done with the current armamentarium is going to benefit at least some people at risk for recurrent or first cardiovascular events.

With regard to risk, I guess all I can leave you with is that when all is said and done, we are going to be faced with making a call as to

the tolerability in, really, just an absolute sense, of some degree of risk. Again, I will say, it is impossible to reach a conclusion, at least on earth, as to the relationship between, for example, a small, admittedly a small, risk of myopathy and an reduced risk of cardiovascular events.

I also want to remind people, furthermore, that we talk a lot about the risk of myopathy with this class of drugs, generally. Number-one thing to remember is that there is absolutely no expectation, regardless of how hopeful we are, that we can obviate all myopathy with statins.

I would offer that, even if we reduced the maximum doses across the board for the marketed statins, we would still see cases.

I also remind you that, in the five-year placebo-controlled trials of statins at a variety of doses, most recently up to 40 milligrams of simvastatin, there have been vanishingly few cases of rhabdomyolysis and, to my knowledge, I don't believe there have been any deaths attributable to drug specifically related to myopathy. Frankly, I don't know that anyone is positive there are any deaths at all attributable to drug.

So let me come to our questions. There is

a long list here. Before the meeting, Dr. Braunstein and I stood and thought that, in the interest of time and in light of the fact that a lot of issues will have been and, indeed, have been discussed prior to this point in the meeting, we don't need to ask--we are not going to ask for a yes or no tally of votes for every single question on this list, unless you feel compelled to, or someone otherwise objects.

Under efficacy, we are essentially asking whether the dose-response data and the overall efficacy data for this drug is such to support the lipid-altering efficacy across the dosage range. It is sort of, in some sense, a no-brainer question. You have seen the data, but it is a formality we need to ask; does the efficacy support essentially the approval for the proposed indications.

With regard to myotoxicity, as I said back at the beginning, a central issue in one of the prime of two reasons that this application was brought before the advisory committee was to, in a public forum, weigh the evidence and have the evidence presented about the myotoxic potential per LDL-lowering efficacy of rosuvastatin and, I

suppose, the absolute myotoxic potential at the highest proposed dose, particularly in light of the postmarketing experience with Baycol and in light of the fact that, at 80 milligrams in trials of rosuvastatin, there were cases of severe rhabdomyolysis and myopathy seen.

So the question I have to you, again, is maybe a relatively simple one. I am happy to hear discussion. Based upon what has been presented to you, are you convinced that the myotoxic potential per LDL-lowering efficacy of rosuvastatin is similar to that of other currently marketed statins.

On the second question under myotoxicity, obviously any comments you have are welcome. With regard to renal effects, we spent a lot of time discussing this and I guess now it is time, really, for a vote. We are going to ask you whether you think, yes or no, the risk of renal adverse events has been adequately evaluated, whether there are any further investigations needed of this, at least it appears now, in the absence of definitive evidence certainly a novel drug effect. Whether or not it is unique to this drug is another question that we are not going to necessarily ask you to

answer but to comment on what you think of those data.

Finally, we are going to ask the question that has been talked about a lot in the discussion about whether monitoring of renal function or, for example, for proteinuria is recommended for this drug or potentially for all statins.

With regard to dosing, I think I need to make a clarification. It sounds, from what we have heard at the table, that there is some confusion. The sponsor has proposed that 10 milligrams be the starting dose for just about everybody, run of the mill, that 5 milligrams be reserved for those people who are on cyclosporine because of the documented seven-fold increase in area under the curve and therefore potential augmented risk for myopathy or other adverse events when the drug is given in conjunction with cyclosporine.

They have reserved 20 milligrams for those people with severe hypercholesterolemia who need--we know going into the game that they are going to need big drops.

The FDA's proposal is simply to say can we add 5 as an option for across the board, as an across-the-board starting dose. It is a dose that

will be available. There will be 5-milligram tablets if this drug is approved. Our question really is why shouldn't physicians be able to choose that as an option in our conceptualization, based upon the desired degree or the required degree of LDL lowering from baseline to goal.

We have asked you to choose, really, between the sponsor's approach and our approach. Finally, we ask the overall recommendation question which is an important aspect usually of these proceedings as to whether you would recommend approval by the FDA of the proposed--across the proposed dosage range for the proposed indications.

We do not, obviously, speak specifically about the isolated hypertriglyceridemia indication. I don't believe we did. So that is included there. I think I would just ask that the committee rule on the data that they have seen thus far.

Thank you very much.

DR. BRAUNSTEIN: Thank you, Dr. Orloff.

Before starting, I have also been asked to remind the panel members as well as everybody else in the audience who has received them to please fill out the surveys concerning the FDA advisory meetings.

Committee Discussion and Questions

DR. BRAUNSTEIN: I thought that what we would do is actually go around and ask for votes on the things that we need to vote on with or without comments. A simple yes or no would be okay but if there are comments, that is appropriate. There are some areas that Dr. Orloff and his group would like to have more input on and we ask for more verbiage there.

If you feel that you want the sponsor or the FDA to respond to a specific question that is going to help you in the decision-making process or in answering these questions, please feel free to ask that also at this time. We want this to be as informed as possible.

What I am going to do is I am going to start off--we will go around the room. I will start with Dr. Kopp to tackle the first question. Then we will go around and then, from there, we will go to Dr. Carpenter to go over the next question, et cetera.

So, Dr. Kopp, if you would weigh in on the first two questions concerning efficacy; has the sponsor provided sufficient evidence to support the efficacy of Crestor in the proposed target

population and, 2, do the efficacy data support a dose response with respect to LDL cholesterol lowering sufficient to justify the use of the 40-milligram dose.

DR. KOPP: I will say yes to both questions.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: Now, are you asking me to move on to the second?

DR. BRAUNSTEIN: No. We have to go around for each question. We are starting with Dr. Kopp for Question No. 1. When we go to a fresh question, we are going to start with you.

DR. CARPENTER: I agree with Dr. Kopp and would answer yes to the questions positively.

DR. BRAUNSTEIN: I also agree; yes, yes.

Dr. Woolf?

DR. WOOLF: So do I.

DR. BRAUNSTEIN: Dr. Hennekens?

DR. HENNEKENS: Yes and yes.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: I would like to talk a little.

DR. BRAUNSTEIN: Go ahead.

DR. FOLLMAN: The thing that really struck

me about the efficacy was there was a lot of discussion about comparing doses of rosuvastatin to other drugs, atorvastatin and so on. To me, that was not the most important issue. What I really felt sympathetic to was the last talk that the sponsor gave where they talked about achieving goals. The me, that is the important thing and when I am evaluating rosuvastatin, I am particularly interested in whether it helps you achieve the NCP goals or not and to what extent it has a better profile than atorvastatin which it was compared to.

So, for me, the most important studies were the dose-titration studies. There we see a significant benefit of the titration when you use rosuvastatin compared to atorvastatin. You get, I think, 96 percent achieving the goal with rosuvastatin compared to about 87 percent with atorvastatin.

So, to me, that is the most important thing about efficacy. When I think about efficacy, that is the reason I agree.

You can also think about the dose-titration studies, though, in terms of information about the 40-milligram dose and whether

we should have that in the armamentarium or not. We saw a lot of, as I mentioned, dose-specific studies and it would be interesting, I think, to imagine what would happen with that dose-titration study if, instead of capping it at 40 milligrams, you capped it at 20. How many would reach the goals at the end of the study.

Actually, with the information the FDA provided, you can look at that. I did a little calculation which suggests if you limit the upper dose to 20 milligrams instead of 40, you get about 91 percent achieving the target instead of 96. So it is still above 90 percent but there is some additional modest benefit of having a 40-milligram dose as opposed to a 20-milligram dose.

So the short answer now is yes, yes for both of those but there is a diminishing benefit at 40 milligrams compared to 20 in terms of dose titration.

DR. BRAUNSTEIN: Thank you.

Dr. Watts?

DR. ORLOFF: Dr. Braunstein, we need a little clarification. I believe, Dr. Follman, you are speaking about the percentages of patients achieving goal within the low-risk category. I

just want to make sure for the record that we are not talking about 96, 91 percent of rosuva patients achieving goal in the high-risk category.

DR. BRAUNSTEIN: Yes; that was, like, 17 percent.

DR. FOLLMAN: Right; this is for the--

DR. ORLOFF: I just wanted to say--

DR. BRAUNSTEIN: Thank you.

Dr. Watts?

DR. WATTS: I will give the short answers and I would like to speak a little as well. Yes, yes are the short answers. My feeling is that we have seven other agents out there that work pretty well when they are used correctly and that the main reason for wanting a drug like this on the market is for the patients who don't respond, don't come to target, with the maximum doses of the other agents.

So worrying about 5 or 10 as a starting dose to me doesn't seem terribly important when we have seven other drugs that we could use for the patients who respond to 5 or 10 milligrams of this drug. But it seems to meet a need for patients who require more potent agents than what we currently have and I think we really need to focus on what

the 20 and 40-milligram dose would do. I think without the 40-milligram dose, there is really very little advantage to this drug over what is already out there.

DR. BRAUNSTEIN: Thank you.

Dr. Wierman?

DR. WIERMAN: Yes, yes.

DR. BRAUNSTEIN: Thank you.

Dr. Levitsky?

DR. LEVITSKY: As a pediatrician, I like to think small. I note that if you start off with an LDL cholesterol which is 150 instead of 190, and you extrapolate, you can do pretty well with 2.5 milligrams, also, so I don't know why we are stopping at 5. This is not going to be a second-order drug. This will just be added to the group.

I am being tongue in cheek about this, but I think that, considering that this drug will be used for the range of people with mild hypercholesterolemia to very severe, we need to have the entire spectrum available. I have, perhaps, some caveats about what I would like in the package labeling for the 40-milligram dose, but I think we need the smaller dose, too.

DR. BRAUNSTEIN: We will come to those caveats under dosing recommendations. So, is your answer yes, yes?

DR. LEVITSKY: Yes.

DR. BRAUNSTEIN: Thank you.

Dr. Neylan is not a voting member of the committee but we don't want to stifle his ability to comment.

So, do you have any comments about No. 1?

DR. NEYLAN: Thank you, Mr. Chairman. As a member of this body without a vote but, like the other members, with opinions I am very happy to chime in. My response is definitely yes, yes, that the sponsor has undertaken yet the most ambitious trials in this area. They clearly, in their magnitude, their scientific rigor, are the state of the art. So, again, efficacy, yes, yes.

DR. BRAUNSTEIN: So we will go to Question No. 2 on safety. We will start with Dr. Carpenter. We will break this down first to the vote that we have to take and then the discussion. So we will ask Dr. Carpenter just to respond to Question No. 1; has the sponsor provided sufficient evidence that the mild toxic potential per LDL-lowering efficacy of rosuvastatin is similar to that of

currently marketed statins.

DR. CARPENTER: I think we have to look at this across doses and, at first glance, eliminate the 80-milligram dose because I think there are clearly other issues with that dose that we all agree are off the table here.

As one extrapolates from the data presented, there is some concern, albeit the numbers are very small, that there is a dose relationship to the incidence of the myotoxicity, whether these, up to the dosage range stated, get above the other statins or not is, from the data I could see, not significant in terms of the a difference.

I would say that the evidence to date would indicate that across 40, up to the 40-milligram dose, we are at levels comparable to the other statins but with some reservation about the 40-milligram dose in that more numbers may bear this to be harder number with more data coming in.

DR. BRAUNSTEIN: So, do you think the potential is similar to the other statins up to the 40-milligram dose?

DR. CARPENTER: I think, at present, there is no difference with the other statins. However,

we may see the 40-milligram dose differ with time.

DR. BRAUNSTEIN: I also say yes, with the current data.

Dr. Woolf?

DR. WOOLF: I concur.

DR. BRAUNSTEIN: Dr. Hennekens?

DR. HENNEKENS: Yes.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: Yes.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: Yes.

DR. BRAUNSTEIN: Dr. Wierman?

DR. WIERMAN: Yes.

DR. BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: Yes.

DR. BRAUNSTEIN: Dr. Kopp?

DR. NEYLAN: Yes. Thank you.

Now we will go back to Dr. Carpenter for the second part of the question. Has the risk of muscle toxicity associated with rosuvastatin therapy been adequately--pardon?

MS. SPELL LeSANE: You forgot Dr. Neylan.

DR. NEYLAN: Actually, I said yes, the non-voting yes.

DR. BRAUNSTEIN: Dr. Kopp?

DR. KOPP: I will add a voting yes.

DR. BRAUNSTEIN: Thank you.

Has the risk of muscle toxicity associated with rosuvastatin therapy been adequately evaluated in the clinical-development program with respect to, among others, the number of patients studied and duration of treatment over the proposed dosage range, special populations such as the elderly, renally impaired or those with comorbid medical conditions and drug-drug interactions?

Again, this doesn't require a vote. It does require any advice to the FDA that you wish to give them along these lines.

DR. CARPENTER: This is a qualified yes but, again, with the comment that I think there is some concern about the 40-milligram dose and this arises, in particular, in some of the special populations. I think a complete and absolute yes on that dosing is going to take some time to bear out as more numbers come in on some of these other groups.

DR. BRAUNSTEIN: I think the risk of muscle toxicity at the 40-milligram dose is still open to question. The data that has been presented has shown that it falls within the range of the

other statins. I do think that after this is on the market and a larger group of individuals with a variety of other comorbid conditions are exposed to it that we need to look at this very carefully.

I am concerned about special populations such as the Japanese population. The pharmacokinetic studies that were performed in Japan did show that the Japanese in Japan had a higher level for a given dose so that I am concerned about certain populations and we may find that, just as certain populations are more susceptible to side effects of different drugs, the Asian Americans, or Asians in general, may have the same problem. So this has to be looked at very carefully.

I would also like to see more extensive evaluation of drug-drug interactions. Certainly, the common ones have been looked at that have been associated with statin myotoxicity and it doesn't look--and, certainly, rosuvastatin falls within the range of what we see with the other statins as far as the effect of other drugs such as gemfibrozil on the drug levels.

But this is something that I think does need to bear watching especially at the

40-milligram level.

DR. BRAUNSTEIN: Dr. Woolf?

DR. WOOLF: There are really three parts to this question. I think A is yes. B, special populations, we have talked about the Japanese but clearly there are other Asian populations and so I think it needs to be broadened to include, obviously, Chinese, Southeast Asian, perhaps people of Indian descent. Who knows? That is going to be carefully looked at and whether it is a genetic issue or whether it is an environment issue needs to be sorted out. The study in Singapore will help it. I think you need to go beyond that.

There are literally thousands of drugs. You can't possibly determine the drug-drug interactions of all the thousands no matter how many people you study premarketing. So it is going to have to be looked at. But, within the confines of a study, I think the sponsor has done about as well as can be expected.

DR. HENNEKENS: I would concur strongly with Dr. Braunstein's position on these matters and also with the caveat that this is the largest and most comprehensive development program of any drug of this class that has ever been undertaken, so it

is not about this drug or about this particular dose as much as the issue that you may not be finding something simply because the expected value is zero in the population that is studied.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: In terms of muscle toxicity in terms of part A, I agree that they have been studied adequately. They met the FDA guidelines for duration and so on. I guess the concern would be if we saw some additional evidence of myotoxicity in the doses between 5 and 40 but, in that range, they are similar to the statins that are approved.

So, if we focus on that range, they have studied enough and I think they have done an adequate job on that account.

In terms of special populations, I have sort of a question, something that I thought about when I was reading this. It seems, in special populations, say, cyclosporine patients who are receiving cyclosporine, what happens is you will notice that the pharmacokinetic parameters are much larger, the area under the curve or Cmax is much larger. Based on that, you decide that the dose should be lowered.

So that sounds like a reasonable strategy. These are relatively rare populations but the way that they proposed doing this, with cyclosporine there was ten-fold increase in Cmax at 10 milligrams compared to health subjects. So they suggested cutting the dose in half to 5 milligrams. I think it would be interesting to study what the pharmacokinetic parameters would be 5 milligrams in cyclosporine and, more generally, for other programs where you are concerned about drug-drug interactions or special populations.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I am favorably impressed with the large body of evidence and the long-term follow up in the populations studied. So I think A is a yes. I don't have anything to add to the concerns about special populations but I think there is more to be learned there and drug-drug interactions don't seem to be an issue other than what has been identified.

DR. BRAUNSTEIN: Dr. Wierman?

DR. WIERMAN: I agree with the comments that have been made by the other members. The only other potential question or comment I had is, as I read the total packet, there was a comment of

drug-drug interactions with birth-control pills changing the AUC of two-fold. But it seemed much more relevant for me, for the population that was going to be treated who are female, what the interactions would be with different combinations of hormone-replacement therapy and that would seem to be of interest especially with all the new information we have about a dose-response curve for hormone-replacement therapy of benefit versus risk.

DR. BRAUNSTEIN: Along those lines, because we didn't talk about this, as I recall the data showed that the levels of hormones in the birth-control pills actually go down with this. So one would ask, does that decrease the efficacy of the oral contraceptives and is that a class action.

DR. ORLOFF: I seem to recall--again, I don't have the labels with me--I seem to recall that that has been found with at least one other statin. I believe it was--the one I am recalling is Lipitor, atorvastatin. Does the sponsor have any comment on that? Also, while Dr. Hutchinson is walking up there, I want to just make one more point of clarification.

In cyclosporine-treated patients, the sponsor is proposing 5 milligrams not just as the

start dose but as the dose, the only dose. So there is no dose beyond that.

DR. HUTCHINSON: I am going to ask Dr. Schneck from our Clinical Pharmacology Department to come up. We did do an ethanol estradiol and norgestrel drug interaction study with rosuvastatin.

DR. SCHNECK: We did a drug-interaction study with a commonly used oral contraceptive in the United States. This is a combination product that contains 35 micrograms of ethanol estradiol and a great increase in concentration over the three-way cycle of the progestin and norgestrel.

[Slide.]

This is the outcome in some eighteen women in which they were dosed to steady state at 40 milligrams in our compound during one of the cycles of the hormone and comparing the outcome from a previous cycle in the absence of rosuvastatin.

The outcome of this trial shows you there is about a 25 percent increase in the circulating concentrations of estradiol in terms of Cmax and AUC and a similar increase in the progestin component of the combination tablet, 23 in Cmax, 34 in AUC. So there is a small increase in the

circulating concentrations of the hormones in the presence of the rosuvastatin, certainly no decrease. Certainly we would not anticipate any reduction in efficacy as far as oral contraception and we would leave it to the judgment of physicians as to what that small increase might mean in terms of long-term exposure on this combination.

DR. BRAUNSTEIN: Thank you.

Dr. Levitsky?

DR. LEVITSKY: Yes, with all the caveats that have been expressed before me.

DR. BRAUNSTEIN: Thank you.

Dr. Neylan?

DR. NEYLAN: Yes to the first and then a special plea for a population near and dear to my heart, the organ-transplant population. That is a group that is roughly a quarter of a million in the U.S. today and double that globally and so a not insubstantial number of patients. It is a group with special needs in terms of lipid lowering. Roughly 80 percent of renal-transplant patients are on lipid-lowering drugs and that is a group of patients in need of better efficacy.

The limited study done in the heart-transplant population which, as a rule, has

less perturbations with lipids than some of the other solid organs, especially kidney, could certainly be amplified. Moreover, we need to better understand interactions with the other emerging immunosuppressants. Cyclosporine now constitutes or is now, in less than half of newly transplanted patients, part of the maintenance regimen.

So, increasingly, other drugs are coming into the forefront and many of these have interactions. So, I would certainly encourage the sponsor to explore this issue in further postmarketing studies.

DR. BRAUNSTEIN: Dr. Kopp?

DR. KOPP: Yes. I would say yes as well. With regard to special populations, I urge the sponsor to look at another Asian-origin population, Native Americans. I was very happy to see that there is a large ongoing trial in ESRD. I think you have 2500 patients. I think that will be important to define what the safe upper limits of dosing would be.

I echo Dr. Neylan's comments about other drugs, particularly tacrolimus FK since it is so closely related to cyclosporine and also serolimus

and knowing more about those interactions.

DR. BRAUNSTEIN: Thank you.

We will go on to IIB, safety in regards to renal effects, the clinical laboratory monitoring in the Crestor development program exposed a heretofore unknown effect of a statin to cause mild proteinuria sometimes associated with microscopic hematuria and mild renal impairment and increased creatinine. This effect appears dose-related in frequency and perhaps severity and reversible on discontinuation of therapy or on lowering the dose of the drug.

Then there are three questions and a comment; a., has the risk of adverse renal effects of rosuvastatin been adequately evaluated over the proposed dose range? b., what further investigations are needed, if any, of this novel drug effect? c., is comment on the data presented suggesting that this may be a statin class effect and d., is monitoring of renal function recommended for this drug or potentially for all statins.

So I will take a crack at these four and then pass it on to Dr. Woolf. Has the risk of adverse renal effects of rosuvastatin been adequately evaluated over the proposed dose range?

I think it has been evaluated and defined that there is a problem, so I think that the risk has been defined.

Certainly, I am very happy to see that almost 900 individuals were on the drug for 96 months. That is very reassuring that it is not going to be a major disaster. So I think it has been adequately defined.

b., what further investigations are needed, if any, of this novel drug effect? I think that this should be examined prospectively in regards to trying to figure out what populations are susceptible to this, if there is any group of individuals that may develop this because of increased susceptibility? Are there medications that these patients are taking, herbs, vitamins, nonsteroidals, some of the other medications that may affect tubular function that, in association with this particular very potent statin, may lead to proteinuria and possibly hematuria?

Defining what the hematuria is due to. I think that we have had a beautiful discussion by Dr. Lewis and also by Dr. Kopp concerning the fact that, in many cases of hematuria, we don't know what the structural defect is that causes the

hematuria. But I think that we should still be looking for that. So I do think that there are some further investigations that should be done in a prospective fashion now that the knowledge is there that this is a potential effect of the drug.

Comment on the data presented suggesting that this may be a statin class effect. I think that it very likely may be and I say that because I am impressed with a couple of pieces of data that were presented. Number one, the lipophilic study showing that this is more likely to get into the renal tubules than most of the other statins that are on the market except for pravastatin which is a weaker drug.

So this is more likely to get to the tubules and get into the tubules. Also it is a very potent drug, as has been shown by the in vitro data. I was also impressed with the melanic acid addition experiment in vitro that this can overcome the tubular readsorption problem induced by the drug suggesting that, really, what we are seeing is a drug that is taken up by the tubules much easier than many of the other drugs and is a very potent inhibitor of the HMG Co-enzyme-A system.

Therefore, if one is able to get a

sufficient quantity of a very potent statin into the tubules, I think it is likely that one will see the same type of effect.

So, although I am just commenting on this because it does say comment, I think that it probably will turn out to be a statin effect from very potent statins that get in the tubules.

Is monitoring of renal function recommended for this drug or potentially for all statins? I don't think monitoring for potentially all existing statins in the market is necessary because we have a lot of a experience with that, so I don't think that one has to go back to that group. For future statins, obviously, the renal effects need to be looked at.

For this particular statin, I do think that monitoring should be recommended for doses of 40 milligrams because of the proteinuria and the hematuria and not knowing really what the long long-term problems associate with that might be. So I do think that it reasonable.

Now, I might say also that it is in this group of patients who are getting the statins that many of them will have comorbid conditions that require renal-function monitoring anyway,

hypertension, diabetes, for instance. But I do think that there should be a clear statement in the labeling that individuals who receive 40 milligrams of rosuvastatin should have periodic monitoring of at least urinalysis for proteinuria and hematuria.

Dr. Woolf?

DR. WOOLF: This is the area that bothered me when I read the briefing documents and my concerns have been partially allayed but not clearly so. The answer to a. is I don't think my concerns really have been adequately evaluated. I don't think that a dipstick urine for protein or blood is adequate and the number of patients who actually got formal urinary protein evaluations and, as we heard, virtually nobody got studies of sediment I think is an oversight.

In fact, I am kind of surprised that this wasn't picked up earlier so that it couldn't have been investigated in the trials that were finishing up toward the end of the evaluation process, particularly those that were started in response to the FDA's comments in 2001.

What further investigations I think we do need to look at the urine sediment for people who do have hematuria. Simply that it is unexplained

is not acceptable. It may be unexplained and benign and it may be unexplained and, five years from now, have some serious consequences. I think we need to know which it is.

The statin class effect, no matter how you slice it and dice it, the 40-milligram dose of rosuvastatin seems to have a greater issues than any of the other doses of the statins that were studied clinically. The in vitro data, I think, is very intriguing and very interesting and very plausible but, as far as I know, humans don't have possum cells. So, perhaps, we need to look at people rather than in vitro data.

So I think that is very interesting. It gives a nice plausible explanation, but I don't think it is adequate. So, in light of a., b., and c., I think that clearly the 40-milligram dose needs to be monitored both in terms of something more than a dipstick urine for renal toxicity.

DR. BRAUNSTEIN: What would you suggest?

DR. WOOLF: I think that some studies actually have to have formal urinalysis and urinary protein in measurements formally normalized to creatinine and then, if one wants to look at breaking down the classes of protein, remember that

I think 22 of the 57 patients where it was looked at actually had a glomerular component, seven or so with glomerular and there was another eight or so mixed. I may have those numbers backwards but, by no means, was it simply tubular dysfunction.

DR. BRAUNSTEIN: That was the baseline.

DR. WOOLF: No; that was the 40-milligram dose.

DR. BRAUNSTEIN: Was it?

DR. WOOLF: Yes.

DR. ORLOFF: Clarification, Dr. Woolf.

DR. WOOLF: Yes.

DR. ORLOFF: It sounded like you were calling for monitoring in ongoing trials as opposed to making a comment on whether and how monitoring should be conducted in, for example, open-market use.

DR. WOOLF: That is a very good point, which you didn't ask us to clarify. But, for sure, it ought to be in monitoring of ongoing trials. I mean, that would be mandatory. I would like to see urine analyses and formal protein measurements or at least spot with creatinine corrections on patients on 40 milligrams at some interval. I agree with our chairman that these are people

likely to have comorbid processes and it may be difficult to sort out what is causing what. But that doesn't mean we shouldn't look.

DR. BRAUNSTEIN: Dr. Hennekens?

DR. HENNEKENS: As I look at the 5 to 40-milligram range of doses, I feel the benefits on LDL, HDL and triglycerides is striking and the hazards on the liver as measured by ALT and the muscles as measured by CK are generally reassuring such that they appear to be as good or even more favorable in some cases than the other marketed statins.

The big issue I grappled with here is that the 20-milligram dose, in my view, is associated with a 0.7 percent rate of proteinuria. This is a low absolute rate but, in my view, it is far higher than the other marketed statins and it is compounded by the fact that when the dose is increased to 40 milligrams, it is up to 1.2 percent.

On its own, I am not concerned about it as part of a development program. However, I am concerned about what impact this will have when millions of people take 40 milligrams of this drug for five to ten years. I am not certain this will

be a reversible tubular defect--not that it won't. I am just not certain. I just don't know.

I would say that the data that I saw suggests diminution, not complete reversibility, of the effect. I would also like to see perhaps more elucidation of this issue ranging from basic research to understand the mechanisms better to clinical studies to quantitate the magnitude and clinical significance of the problem. My concerns here do relate specifically to the 40-milligram dose. So I would perhaps want to see more cogent data beyond just monitoring the trials which have a relatively low sample size of people on the 40-milligram dose to basically better understand and quantitate the problem before deciding on a solution that may or may not be adequate.

DR. BRAUNSTEIN: So, if I understand your responses to the questions, a., has the risk of adverse renal effects of rosuvastatin been adequately evaluated over the proposed dose range. Do you think it has been adequately defined?

DR. WOOLF: Well, the risk has been adequately evaluated in the sense that I now believe there is a risk at the 40-milligram dose.

DR. BRAUNSTEIN: And the further

investigations, you noted. You didn't know whether you thought that this was statin class effect.

DR. WOOLF: I did say, in my reading of the data, I would say that it seems to be not necessarily peculiar to this drug but peculiar to the dose of the drug, 40 milligrams and above, not to this drug, even.

DR. BRAUNSTEIN: You would favor monitoring at the 40-milligram dose.

DR. WOOLF: I think I am saying that, on the one hand, monitoring may be too much but, on the other hand, it may be too little. I am still not basically getting my hands around both the mechanisms as well as the magnitude of the issue. So, in some ways, if there were a way to try to suspend monitoring as a solution for this because it may turn out, with further evaluation, that this is less of a problem than it appears and, therefore, monitoring wouldn't be necessary.

On the other hand, if further data support the magnitude of the problems would be greater, than monitoring might not be enough. So I am just not sure.

DR. FOLLMAN: I broadly agree with what Charlie mentioned. In terms of part a., has the

risk of adverse events been adequately evaluated, for the other safety parameters over the range of 5 to 40 milligrams, I think we have a flat-dose response curve and there is not a concern about muscle toxicity or liver toxicity.

Here, though, in terms of the kidney, we have a concern at the 40-milligram dose. The real issue, I think--and so this is unlike the other safety parameters. The 40-milligram dose is, I think, the thing we are all focusing on, has it been adequately characterized.

Your point about the risk is, I thought, well put that we are aware now of a risk that we didn't know about before. This had not occurred in the other statins. The real issue to me is whether we have enough information to feel comfortable that there won't be clinical events related to the kidney once it is licensed.

That is something we don't really know now. The only way to get knowledge about that is to do large studies. Charlie mentioned that this is a relatively rare event probably and the only way we are going to get information on it is to study it in a lot of people.

So, to finish up, I guess, Part a., the

risk has been adequately characterized in terms of these laboratory parameters. The clinical sequelae we don't know yet. So, for part b., what further investigations might be needed, I think the large clinical-trials program that they have mentioned earlier today, probably over 20,000 people that they are going to be studying, would be good for a step in that direction, I think, maybe the only step that needs to be done in terms of monitoring clinical consequences for this problem.

In terms of Part c., whether this is a statin class effect, when I read this, I thought, I don't really know one way or the other. But I also thought it didn't really matter because we don't see any evidence of this in any of the other statins. This is only brought to our attention because of the high dose. So, whether or not it is a statin class effect doesn't matter to me. We see it here at 40 milligrams, to some extent, and certainly at 80 milligrams. That is what we need to focus on, whether we have clinical events, an increased rate of clinical events for this.

Then, finally, I would agree that monitoring of renal function is probably needed if we are going to approve this study. Eventually, it

might turn out with more information. We know that it is unnecessary. Charlie was saying he just didn't know at this point and I agree, we don't know. So, to be on the safe side, we should monitor now. Eventually, it might be viewed that it is unnecessary in some populations or maybe across the board.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: I don't think the adverse renal effect has been explored adequately at the higher dose. I agree with Dean. I don't know whether this is a class effect and I don't know that it matters. If it is a class effect, it seems to be related to the potency of the drug and the low lipophilicity. So it doesn't seem to apply to the other statins that are in clinical use.

If I were taking this drug in a 40-milligram dose or if I were using it in my clinic, I would want a baseline serum creatinine and a baseline urinalysis. Periodically, I would want a dipstick urinalysis and, if I saw 2-plus protein or 1-plus blood or both, then I would at least repeat that urinalysis. If those findings were there on repeat, then I would want to quantify my urinary protein and renal function.

So, in clinical practice, until there is more data for safety, I would recommend monitoring. I don't know that it needs to be monitored with quantitative urinary protein because the dipstick seems to be sufficiently sensitive to let you know where there might be a problem.

I think there is probably some data in the existing dataset that would help us. I asked about the time of the appearance of this. It looks like there were several hundred patients who had proteinuria, several hundred patients who had hematuria, and I am not convinced that the sponsor has looked adequately at the existing data to convince me that this is a transient phenomenon versus a fluctuating phenomenon and that longer-term use might show that there is a problem.

I think that, in the ongoing large trials, it should be possible to answer that question and also do more detailed analysis to find out if there are other changes in tubular function that emerge in patients who show proteinuria. I think that it may turn out to be very reassuring data from the existing set and from the ongoing trials, but, until we have that reassurance, I think patients on the high dose should be monitored.

DR. BRAUNSTEIN: Dr. Wierman?

DR. WIERMAN: I agree with the comments that Dr. Watts just made. Perhaps, unlike some of the other members, I think that additional research does need to be done at the basic level because I think, if we understand the mechanism of how this agent is working at the tubule, you may be able to predict which patients might be at risk and what drug-drug interactions it may occur in.

So I think that, as well as the careful monitoring of patients initially as the drug gets approved and in ongoing studies, I think further basic studies to understand the molecular mechanisms may provide the insight then to target patients and to use the drug most safely.

DR. BRAUNSTEIN: Dr. Levitsky.

DR. LEVITSKY: I agree that the risk of adverse renal events has been adequately evaluated up to the highest dose range, the 40-milligram dose range, at which point I think that further evaluation is necessary and those further evaluates should consist of the large-scale clinical surveillance studies that are under way as well as further in vitro studies.

The in vitro studies that were presented

are convincing for some sort of statin class effect but the human studies do not yet support this, so they need to be carried further. I am concerned that this is an important issue because, no matter what dosage range is suggested by the FDA, many of the other drugs in this class may well be used outside those dosage ranges so, knowing this is a class effect is an important thing for physicians, particularly specialists, using these agents.

Then, finally, I certainly would recommend monitoring of renal function as was suggested before in patients on the highest dose of these drugs.

DR. BRAUNSTEIN: Dr. Neylan?

DR. NEYLAN: I agree that the approximate low-level risk of renal dysfunction has been characterized, although I do believe that there is much, as the previous panel members have suggested, that can be done to further understand, both at the level of prospective clinical trials, postmarketing surveillance and, of course, further preclinical data.

As far as the types of further investigations, I am certainly intrigued by the

hypothesis put forth by the sponsors as to a mechanism for changes in tubular handling of protein. I struggle, though, to make that model answer all the questions regarding the renal picture as a whole and especially hematuria which I guess I have sort of latched onto especially today.

So I would encourage other looks, other relevant models, to look at the possibility both at the tubular epithelial level and other parts of the kidney that there is not some evidence for ongoing increased turnover or inflammatory process.

Is this data suggestive of a class effect? My gut feeling tells me yes, although I certainly do not think there is enough here to warrant stating that or carving it in stone. I do think it is very important to understand this. As Dr. Levitsky says, the use of all these agents will be broadly applied and used increasingly in the coming years and especially given the potential interactions and different handlings within special populations. Despite current dose ceilings for these other agents, we are likely to see a wide variety of increased exposures and I think it behooves the community to be on the lookout for this and for all of us to better understand if

there is, indeed, a class effect or not.

Finally, monitoring, should it be recommended? My bias as a nephrologist is that, in this population of patients, in general, renal function in older patients with multiple comorbidities for cardiovascular disease and nephrosclerotic disease do warrant periodic monitoring if only once a year for serum creatinines and urinalyses. I agree with Nelson's observation that, were I starting this in the clinic, and now as I think about it for other statins, obtaining a baseline urinalysis and a serum creatinine seems a very modest and quite acceptable start for this.

DR. BRAUNSTEIN: Thank you.

Dr. Kopp?

DR. KOPP: For Question a., I think the studies to date have been adequate but could be improved. I will touch upon some of the themes that we have heard about already. Is this a functional defect? I think that is possible but I am not sure that that is all that is going on. Is there a structural problem? I gather we have had just one renal biopsy available in somebody who has both proteinuria but not renal failure and is this

progressive as we follow patients out three and four and five years.

Again, two issues that were talked about, how do we understand the glomerular proteinuria that apparently is present in about a third of the patients, either pure glomerular or mixed, a third of the patients with proteinuria that we were told about and how do we understand hematuria. Is it functional, as Dr. Lewis mentioned can happen, or is it something else?

In terms of further investigations, I think animal studies might add something here. We heard that a variety of statins cause epithelial-cell damage but maybe we can learn something more. Maybe we can better understand is there a glomerular-disease element as well using that model.

In terms of human investigations, I think I would like to see continued follow up on patients beyond 96 weeks and I would argue that we should be doing more renal biopsies in those patients who have unexplained proteinuria possibly as part of a research protocol rather than from pure clinical indications to try to increase that n of 1 and get a sense of are there patients who do have

tubular-cell atrophy and so forth at a relatively early stage before they have a rise in creatinine.

In terms of a class effect, like, I think, like everyone here, it is possibly true that it is a class effect and it is also possible that rosuvastatin has an additional action and I think it is very hard to sort those two out.

In terms of monitoring, I would first say that, yes, for 40 milligrams but I would also say that there are patients who may only be getting 5 milligrams. But if they are getting cyclosporine and their AUC is seven-fold elevated, they may have drug levels comparable to 40 milligrams. So I think the package label ought to say something about patients at a high risk for toxicity either because of a change in the AUC, the PK, or, alternatively because of a second agent that might be additive or even synergistic in terms of tubular toxicity. We will have to leave it up to the clinician to use good judgment about how to interpret increased risk.

Like the others, I would like to see, at a minimum, a creatinine and an urinalysis. I would argue a protein-to-creatinine ratio, particularly in this population that we talked about with

diabetes and hypertension is pretty much standard of care and then periodically--and I don't know what the right period is; would it be every six months or every year--to repeat at least the urinalysis or the protein-to-creatinine ratio.

DR. BRAUNSTEIN: Thank you.

Dr. Carpenter?

DR. CARPENTER: With respect to a., I think yes, the studies presented have been adequate to define the risk of the renal issues that we have been discussing. However, we have not defined the lesion. I think that is where our level of uncomfortableness is here, that we know something is going on but we don't really have a good handle on precisely what it is. Thus further investigations, I think, would be most useful and I particularly appreciate the animal studies effect.

I think at this point the data done in the OK cells suggesting that this is a statin class effect can only be taken at this point as a suggestion. It is interesting but this may be something that is true across statins but is perhaps even unrelated to the global renal effects that we are seeing.

The point that could be inserted here,

too, is the 40-milligram dose does seem to be that which, as others have mentioned, is where we are most concerned. That would lead into the monitoring question and I would address this at two levels; first, monitoring with respect to clinical use. I would agree with Dr. Watts' suggestion that preliminary investigations of creatinine levels as well as subsequent dipstick urinalyses would probably address that and particularly at the 40-milligram dose level.

As I recall, although the numbers of patients in the 40-milligram categories were actually quite good because of the inclusion of the back-titration subjects, there were probably lower numbers in the 20-milligram dose than in any other dosage category so I still have some reservation about eliminating monitoring in that category simply because of the limitations of the numbers.

Finally, at a second level of monitoring, as the sponsors indicated they were already doing, I think it is a great idea, in continued trials, to examine fresh urine sediment as another approach to trying to define what the lesion is.

DR. BRAUNSTEIN: Thank you.

We will move on to the third issue which

concerns dosing recommendations. We will take all of these as we go around as a group. No. 1, are the data adequate to support the 5, 10 or 20-milligram doses as a safe start dose. 2, are the safety data adequate to support a maximum dose of 40 milligrams a day. To a certain extent, we have already discussed this but I think it is worthwhile saying yes or no.

3, does the committee recommend a range of start dosages--that is 5 to 20 milligrams--in which an individual may be initiated on therapy based on CHD risk, baseline LDL cholesterol levels and target LDL cholesterol or, alternatively, should there be a fixed start dose of 10 milligrams recommended for the general population with 5 and 20 milligrams reserved for special circumstances as proposed by the sponsor.

Dr. Woolf, will you handle those?

DR. WOOLF: I'll try. I think that we have beaten No. 1 to death. It is more than adequate data that these are safety dose. The 40-milligram dose is a very valuable addition to an armamentarium that desperately needs some augmentation at higher efficacy. So, with data we have, despite what I said before, I think that, in

this population, I would rather run the risk of some unexplained proteinuria than cardiovascular disease. So the answer to that is yes.

The answer to 3--

DR. WOOLF: 3 and 4 are together--is somewhat difficult. Those of us who have been around long enough remember that we were told we needed to titrate statins. That is what we were brought up with and that is what the general physician in primary practice was told. And the company, the industry, did a very good job of that. So now the industry is trying to say, well, we made a mistake. We now know better. We should have a fixed dose.

So we are betwixt and between. The notion, then, of saying, well, yeah; 5 is effective. 10 is more effective. So why don't you start with 5. That gets us back to titration and people are not going to get titrated. Even in good studies done by cardiologists, done by endocrinologists, who should know what they are doing, it ain't happening.

So I would go along with starting with the 10-milligram dose to start in the non-high-risk patients and back titrate down if I don't need to

rather than try to convince somebody to go up because that is not going to happen. So I would like to see the start dose at 10. The safety profile seems to be comparable to 5, at least in the several thousand patients that have been presented to us.

I would reserve 20 and, perhaps, even 40 to start doses for people with high and ultrahigh risk doses--risk, rather.

DR. BRAUNSTEIN: Thank you.

We are actually going to go out of order because Dr. Wierman has to leave. So I am going to ask her to answer III and also to weigh in on IV before you leave.

DR. WIERMAN: My answers are for III-1, yes; I think the data are adequate to support the doses, the safe-start doses, any of the start dose and to support the maximum of 40 milligrams daily.

I go back and forth on whether or not we should recommend the 10 versus the fluctuating dose. I am swayed by the arguments that say that people don't switch the doses once they start and I think we should do a better job as clinicians and educators of dosing down as well as dosing up. So I would favor the 10 start dose. I guess that is

the end of that. The overall answer for the recommendation to IV, I vote yes.

DR. BRAUNSTEIN: Thank you.

We will go back to Dr. Hennekens.

DR. HENNEKENS: Question 1, I think the answer is yes. Question 2, the answer is yes with the caveats we have discussed. With regard to Nos. 3 and 4, I feel that the same distinguished panelists who published on the low percentage of people achieving goals also in their publications is the large number of patients who would benefit from statin therapy and who were not treated at all. So my own view of these questions, 3 and 4, would be that whatever the sponsors and agency finally decide are going to do the most good for the most people by getting more people on statin therapy would be the best strategy to achieve.

DR. BRAUNSTEIN: Thank you.

Dr. Follman?

DR. FOLLMAN: For the first question, I would say yes, they are fine start doses. The second question, has 40 milligrams daily be justified; I would say probably provided we are monitoring that and the ongoing studies don't show anything alarming. And I favor a 10-milligram

start dose for the reasons Dr. Woolf mentioned. I think, for whatever reason, if we titrate, if there is more titration involved at the end of the day, there will be fewer people achieving goals.

So, if we have a 10-milligram start dose, I think we will have better health in the people who are getting the statin.

DR. BRAUNSTEIN: Thank you.

Dr. Watts?

DR. WATTS: The answer to 1 is yes. The answer to 2 is yes. I like the Hennekens Principle for the start dose. I think cost should also be considered here if the 5-milligram tablet would be half the price of the 10-milligram tablet, then maybe that would weigh in for a lower dose. But the practical issues of titration not happening are also there.

I think, certainly, the 20 and 40-milligram start doses should be start doses only for high-risk populations.

DR. BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: 1 is yes. 2 is yes. 3 requires a digression which is that, as a pediatrician, I have watched with bemusement over the years as internists finally came to the

conclusion that 90-year-old 90-pound ladies were not the same as 300-pound 30-year-old guys when it came to drug doses.

You guys are moving in the right direction, But I am worried at the idea that you all still can't titrate a dose based upon response. I would like to have 5-milligram doses because there are so many drugs now that we don't have adequate dosing for because you all who make up larger parts of the population don't need them.

So I really would like to have a titration ability but I will defer to you. You are going to be using these drugs more than we will. It looks as if the 5 is going to be something you have to call the company and get special permission for, not something that is going to be available in every CVS.

DR. BRAUNSTEIN: We are getting a lot of head-shaking that says no.

Dr. Neylan?

DR. NEYLAN: They may score the tablet, of course. Yes to the first, yes to the second and to 3, 4, I would sort of split the difference and say, "Suggested 10-milligram start dose (5 to 20)," so start off with the suggestion of the fixed start

but in the dosing section give some rationale for why there might be some flexibility.

DR. BRAUNSTEIN: Thank you.

Dr. Kopp?

DR. KOPP: I say yes to 1 and yes to 2. And, for the others, it is too complicated for me. I pass.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: I say yes to 1. On Question 2, I think there is concern enough at the 40-milligram dose when attempting the impossible risk-benefit analysis of the standard variety low-risk patient that, at that high level, the increment over the 20-milligram dose seems minimal, yet the risk may increase substantially so that, in the nonhomozygous familial-hypercholesterolemia-dose subjects, there may be some question about the max dose there.

I think, otherwise, the safety data is reasonable and the risk-benefit analysis in the severe patients is also reasonable. With respect to 3 and 4, I like the "split the difference" approach suggested by Dr. Neylan. I had a question reflecting Dr. Levitsky's comments as to the youngest patient that has been treated with

these drugs and, despite the fact that the market is obviously limited in pediatrics, in the future, with obesity running rampant, this may change.

I just wondered if there was any data from the sponsor on pediatric utilization here.

DR. BLASETTO: The data that we had in the homozygous familial hypercholesterolemia, we did allow patients in below the age of 18 and we actually studied 80 of those patients in homozygous FH.

[Slide.]

This is the result that we saw in LDL-C reduction. We had a 20 percent reduction in LDL-C in homozygous FH patients below the age of 18 and up to the 40-milligram dose in a forced titrated study at 26 percent mean LDL-C reduction which is very favorable reduction in this severe homozygous FH population of patients and below the age of 18.

DR. BRAUNSTEIN: Thank you.

I think the data are adequate to support the doses of 5, 10 or 20 in various populations as safe start doses. I do think that the safety data has been adequate to support a maximum dose of 40 milligrams a day with all the caveats that have been said.

In regards to whether to recommend a fixed dose or titration, I am a bit torn here from the standpoint that if one looks at the 5-milligram dose, starting dose, there is a 43 percent reduction in LDL cholesterol which is actually greater than or equal to at least all the other statins on the market and their starting dose. So 5 milligrams is at least equivalent.

Also, I like the idea of titrating based on risk factors and target levels, especially in the primary prevention population where, although the slope of relationship between cardiovascular events and mean LDL cholesterol levels is upward, it is still certainly flat in comparison to secondary prevention where I would advocate a higher dose and getting a cholesterol down as far as possible.

Nevertheless, I do think that, in order to do the greatest good for the greatest number, if you will, that a 10-milligram fixed dose is a reasonable suggestion. I would also say that a 5-milligram starting dose is also a reasonable way to go and to titrate up and to give the clinician the ability to go either way. So either 5 milligram or 10 milligram and provide that 10

milligram does provide increased efficacy.

From a safety standpoint, the two are very equivalent so I am not really worried about the safety. So the risk-benefit ratio probably favors the 10-milligram dose although we don't have data on millions and millions of people for a score of years or so. So saying that 10 milligrams is safer than 5 milligrams is, as I said, based on somewhat limited data but, thus far it does look that way.

So we will go to the final question which is the overall recommendation. Before going to that, we did not discuss today in any detail, although the committee did receive the details about isolated hypertriglyceridemia. First of all, does the committee want to ask any questions about that or do you feel that you are knowledgeable enough, based on both the sponsor's material that was sent out and the FDA's material that was sent out to be able to include that in the overall recommendations as it is stated here or do you want additional information presented?

Does anybody want anything additional? Dr. Levitsky?

DR. LEVITSKY: I read the sponsor's statement and showed that it looked as if

triglyceridemia was somewhat improved but, if we are going to include that, I would like to have some further discussion, I think.

DR. BRAUNSTEIN: Okay. Can you briefly summarize the isolated hypertriglyceridemia data?

DR. BLASETTO: Could I have the Type IIb and IV, please, split.

[Slide.]

We performed a dose-ranging study in patients with hypertriglyceridemia which included patients with Type IIb and IV hypertriglyceridemia. It was patients at randomization had triglycerides between 300 and 800 milligrams per deciliter. This is the response we saw. We did stratify the patients by IIb and IV and the response in triglyceride reduction in doses versus placebo, 5 to 40-milligram doses in the triglyceride reduction.

So we saw reductions in triglycerides both in IIbs and IVs. The Type IV patients had higher baseline triglycerides expected had a large reduction in triglycerides as would be expected.

DR. BRAUNSTEIN: FDA reviewers, do you have any other comments about the triglyceride data, especially the Type IV which is the pure

situation?

MS. MELE: I am just trying to remember the results for this. I think what we saw were when the HDL values were higher or lower, we were getting higher and lower responses based on the level of HDL. I was just trying to look that up.

When HDL was less than 39, we got a much bigger response in triglycerides than when it was higher than 39. So that was one thing we noticed. The dose response, the biggest difference was between 5 and 10 and then it started to level off across 20, 40 and 80.

DR. BRAUNSTEIN: You note, in the medical review, that the mean dose-response curve was flat at doses about 10 milligrams.

MS. MELE: Right. That is about right.

DR. BRAUNSTEIN: But you did conclude that it was efficacious for that indication.

MS. MELE: Yes. It just didn't get more lowering when you went above--you got a little bit with 20 but certainly not with 40.

DR. BRAUNSTEIN: Is that a sufficient summary? Great. Then let's go on to the final question. We will start with Dr. Hennekens, the overall recommendation. Do you recommend that

Crestor 5 to 40 milligrams be approved by FDA as an adjunct to diet for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia and isolated triglyceridemia and for the treatment of patients with homozygous familiar hypercholesteremia as an adjunct to LDL apheresis or if apheresis is not available?

DR. HENNEKENS: Yes.

DR. BRAUNSTEIN: Thank you.

DR. BRAUNSTEIN: Dr. Follman?

DR. FOLLMAN: Yes.

DR. BRAUNSTEIN: Dr. Watts?

DR. WATTS: Yes.

DR. BRAUNSTEIN: Dr. Levitsky?

DR. LEVITSKY: Yes.

DR. BRAUNSTEIN: Dr. Neylan?

DR. NEYLAN: Yes.

DR. BRAUNSTEIN: Dr. Kopp?

DR. KOPP: Yes.

DR. BRAUNSTEIN: Dr. Carpenter?

DR. CARPENTER: Yes.

DR. BRAUNSTEIN: I say yes.

Dr. Woolf?

DR. WOOLF: Yes, with a caveat and that is there is no evidence that the 40-milligram dose is

any greater than 20 or perhaps even 10 for isolated hypertriglyceridemia. I think that the range should not be 5 to 40 but should be 5 to 10 or, at most, 5 to 20.

DR. BRAUNSTEIN: Any other comments or questions from the committee?

Summary

DR. BRAUNSTEIN: Let me just try to briefly summarize what the committee's responses have been. In regards to efficacy, the committee unanimously felt that the sponsors had demonstrated that Crestor was efficacious and sufficiently efficacious all the way up to 40 milligrams to warrant including a 40-milligram dose. So the answer was unanimously yes.

In regards to mild toxicity, it was also unanimously felt that the sponsor provided sufficient evidence concerning the myotoxic potential per LDL-lowering efficacy of rosuvastatin and that is similar to that of currently marketed statins.

In regards to the question of has the risk of muscle toxicity associated with rosuvastatin therapy been adequately evaluated in the clinical-development program with respect to, among

others, numbers of patients, special populations, drug-drug interaction. Basically, the answer there was yes with some caveats; that is, if there needs to be some more potential drug-drug interaction evaluation in follow up.

In regards to renal effects, has the risk of adverse renal effects if rosuvastatin been adequately evaluated over the proposed dosage range. The majority of the committee felt that it had been adequately evaluated; that is, the risk had been defined, that, unfortunately, the mechanism has not been as well defined.

There was rather widespread encouragement that further investigations are needed, both at the basic and the clinical level and to look at some animal models. I might mention that Dr. Orloff indicated in a discussion that, perhaps, perfusion of isolated tubules or perfusion of isolated kidneys might provide some additional information especially in comparison to the other statins because one doesn't have some of the adsorption issues.

As far as the data suggesting that this may be a statin class effect, it is suggestive but not proven. Is monitoring of renal function

recommended for this drug or potentially for all statins? The committee really limited its concerns to this drug and felt that, at the 40-milligram dose, that clearly there should be some monitoring of renal function, at a minimum, baseline creatinine and urinalysis. There is a plea to consider doing an albumin-creatinine ration in the urine to start with and then periodic evaluation. That evaluation has included creatinine and at least a dipstick urinalysis if not a full urinalysis all the way to doing periodic albumin-creatinine determinations.

So we were certainly not unanimous on that except that we were unanimous that at least a 40-milligram dose does warrant at this time further evaluation after it is out on the market.

As far as dosing recommendations are concerned, we agreed that 5, 10 and 20-milligram doses were safe start doses in the various populations that were described. Are the safety data adequate to support a maximum dose of 40 milligrams a day? And the committee was unanimous on that in the affirmative.

Does the committee recommend a fixed dose versus titration? We were split on that. I think

most of us felt that the 10-milligram fixed dose is a very reasonable compromise in getting physicians to prescribe it, number one, getting patients to take it without the hassle required for titration. No. 3, that it is safe and the present data indicates that it is as safe as the 5-milligram dose.

So I think the majority of the committee, although I think they would wish to see titration ideally feel that a 10-milligram fixed dose is a reasonable start. There is also the opinion of several members of the committee that the clinician should be given an option to start at 5 milligrams as well as 10 milligrams and that the data be provided in the package insert and with educational sessions to discuss both the 5 and 10-milligram start doses.

Finally, the overall recommendation was unanimous that this should be approved.

With that, we will bring the session to close. I thank the panel members, the FDA for a wonderful analysis and certainly to the sponsors for a beautiful presentation.

Thank you.

DR. ORLOFF: Let me add my thanks to all

involved, FDA reviewers, the sponsor and their presenters and the committee for a great deal of good work and worthwhile commentary. Thank you very much.

[Whereupon, at 3:30 p.m., the meeting was adjourned.]

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