UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

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THURSDAY,

MARCH 6, 2003

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The meeting was convened in the Ballroom of the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland, at 8:30 a.m., Michael Camilleri, M.D., Acting Chair, presiding.

PRESENT:

MICHAEL CAMILLERI, M.D.	Acting Chair
TOM PEREZ, M.P.H.	Executive Secretary
SUSAN COHEN	Consumer Representative
BYRON CRYER, M.D.	Member
RONALD P. FOGEL, M.D.	Member
JOHN T. LaMONT, M.D.	Member
ROBERT A. LEVINE, M.D.	Member
DAVID C. METZ, M.D.	Member
MARIA H. SJOGREN, M.D.	Member

CONSULTANTS (VOTING):

HOWARD McLEOD, PHARM.D.
RUTH HOFFMAN
MICHAEL PROSCHAN, Ph.D.
ZERUESENAY DESTA, Ph.D.

MEMBERS OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

(VOTING):

DAVID KELSEN, M.D.
OTIS BRAWLEY, M.D.

FDA:

GARY DELLA'ZANNA, D.O., M.Sc.
FLORENCE HOUN, M.D.
VENKHAT JARUGULA, Ph.D.
ROBERT JUSTICE, M.D.
JOYCE KORBICK, M.D.
NARAYAN NAIR, M.D.
HUGO GALLO TORRES, M.D., Ph.D.

I-N-D-E-X

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

(8:34 a.m.)

CALL TO ORDER, INTRODUCTIONS

CHAIRPERSON CAMILLERI: My name is Michael Camilleri. I am the Acting Chairperson for this Gastrointestinal Drugs Advisory Committee meeting. We are going to be discussing today the new drug application, NDA 21-549, on EMEND, which is aprepitant.

I want to remind the board members, please, to speak directly into the microphone and to remember to switch the microphone off when you are done with your deliberations.

The next item of business, really, is to invite the board members to introduce themselves. So I would like to start.

DR. HOUN: Hello. I'm Florence Houn. I'm the Office Director for FDA's Drug Evaluation 3 Office. Thank you.

DR. JUSTICE: Hi. I'm Robert Justice. I'm the Director of the Division of Gastrointestinal and Coagulation Drug Products.

DR. DELLA-ZANNA: Hi. My name is Gary Della-Zanna. I'm a medical officer in the Division of Gastrointestinal and Coagulation Drug Products.

DR. JARUGULA: Hi. I'm Venkhat Jarugula, clinical pharmacology and biopharmaceutics on the NDA.

MS. HOFFMAN: Hi. I'm Ruth Hoffman, patient advocate, National Director of Candlelighters Childhood Cancer Foundation.

DR. SJOGREN: Hi. I'm Maria Sjogren. I'm a gastroenterologist and hepatologist. And I work at Walter Reed Army Medical Center in Washington, D.C.

MS. COHEN: I'm Susan Cohen. I'm the consumer member, and I just had a colonoscopy.

DR. FOGEL: Good morning. I'm Ron Fogel. I'm a gastroenterologist, division head at Henry Ford Health System in Detroit.

DR. CRYER: Good morning. I'm Byron Cryer, member of the Gastrointestinal Drug Advisory Committee. I am a gastroenterologist. I am from the University of Texas, Southwestern Medical School in Dallas.

CHAIRPERSON CAMILLERI: I'm Michael

Camilleri. I'm a member of the Gastrointestinal Drugs Advisory Committee. I am a gastroenterologist. And I practice at Mayo Clinic in Rochester, Minnesota.

SECRETARY PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. METZ: I'm David Metz. I'm at the University of Pennsylvania at Philadelphia and on the advisory committee.

DR. LEVINE: I'm Bob Levine from Syracuse, New York at the Upstate Medical University, State University of New York. I'm a gastroenterologist and a hepatologist.

DR. LaMONT: My name is Tom LaMont. I am from Beth Israel Deaconess Medical Center in Boston. And I am a member of the FDA committee.

DR. KELSEN: David Kelsen, medical oncologist. I'm from Memorial Sloane-Kettering in New York.

DR. BRAWLEY: I'm Otis Brawley. I'm a medical oncologist at Emory University.

DR. McLEOD: I am Howard McLeod, a clinical pharmacologist in oncology at Washington

University School of Medicine in St. Louis.

DR. DESTA: Zeruesenay Desta from Indiana University, Division of Clinical Pharmacology. I am a clinical pharmacologist and member of the advisory committee.

DR. PROSCHAN: And I'm Mike Proschan. I am a statistician with the National Heart, Lung, and Blood Institute.

CHAIRPERSON CAMILLERI: Thank you very much. At this point I would like to turn the proceedings over to the executive secretary for statements.

SECRETARY PEREZ: Thank you.

MEETING STATEMENT

SECRETARY PEREZ: 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 interest 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. Byron Cryer has been granted waivers under 18 USC 208(b)(3) and under 21 USC 355(n)(4), an amendment of Section 505 of the Food and Drug Administration's Modernization Act for ownership of stock in the sponsor valued at less than $5,001 and for unrelated consultant for a competitor. Dr. Cryer receives less than $10,001 per year.

Dr. David Kelsen has been granted waivers under 18 USC 208(b)(3) and under 21 USC 355(n)(4), an amendment of Section 505 of the Food and Drug Administration's Modernization Act for ownership of stock in the sponsor valued between $5,001 and $25,000.

Susan Cohen has been granted waivers under 18 USC 208(b)(3) and under 21 USC 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of

stock in the sponsor valued between $5,001 and $25,000.

Dr. Camilleri has been granted a waiver under 18 USC 208(b)(3) for membership on a competitor's advisory board through a contract with his employer. This interest generates less than $10,001 per year.

Dr. David Metz has been granted a waiver under 18 USC 208(b)(3) for his membership on the sponsor's speakers' bureau. His lectures generate income greater than $10,000 per year.

Dr. Robert Levine has been granted a waiver under 21 USC 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in the sponsor valued at less than $5,001. Because this stock interest falls below the de minimis exemption allowed under 5 CRF 2640.202(a)(2), a waiver under 18 USC 208 is not required. 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 the event the discussions involve any other products or forms 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 product they may wish to comment upon.

Thank you.

CHAIRPERSON CAMILLERI: Thank you, Tom.

I would now like to invite Dr. Robert Justice to make his opening comments.

OPENING COMMENTS

DR. JUSTICE: Good morning. On behalf of the division, I would like to take this opportunity to welcome the committee members and consultants to today's meeting. We appreciate the time that you are taking from your schedules to provide us with advice.

On today's agenda is a new drug application for EMEND or aprepitant capsules followed

by a brief closed session later this afternoon. As you will hear, the new drug application seeks approval for EMEND for the indication of EMEND in combination with other *antiemetic medications. It is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

As you listen to the company's and FDA's presentations, we would like you to keep the following questions in mind for discussion this afternoon.

Go to the first slide. The first one is, has the aprepitant regimen been demonstrated to be effective in the prevention of nausea and vomiting in the acute phase and in the delayed phase?

The second question is, is the designation of "highly emetogenic chemotherapy" appropriate given the regimens used in the clinical studies?

Next question, please. The third question is, can the recommended regimen be expanded beyond that used in the clinical studies to include the use of any 5-HT_3 antagonist as part of the aprepitant

regimen? If not, what additional studies would you recommend?

The fourth question is probably the most important today. The preamble to that question is that aprepitant is an inhibitor of the CYP3A4 metabolic pathway. For chemotherapeutic drugs that are metabolized by this pathway, moderate inhibition of their metabolism could result in serious or life-threatening toxicity.

Next slide. The first part of the question is, the applicant has analyzed the safety data by chemotherapy regimen and a significant number of patients received etoposide, vinorelbine, or paclitaxel, which are substrates for CYP3A4, in combination with cisplatin and the aprepitant regimen.

Is this data sufficient to support the safety of aprepitant in combination with these drugs? If not, what additional studies would you recommend and should these studies be done pre-approval or post-approval?

Next slide. The second part of the question is, few or no patients received docetaxel,

vinblastine, vincristine, ifosfamide, irinotecan, or imatinib, which are also substrates for CYP3A4, in combination with cisplatin and the aprepitant regimen.

The docetaxel drug-drug interaction study has accrued only five patients to date. Is there sufficient data to support the safety of aprepitant in combination with these drugs? If not, what additional studies would you recommend, and should these studies be done pre-approval or post-approval?

Next slide. And, finally, does the committee have specific concerns regarding potential drug-drug interaction with other chemotherapeutic agents or other drug classes? If yes, please discuss them and whether any additional studies are recommended.

So those are the questions to keep in mind. With this introduction, I think we can hear the company's presentation.

CHAIRPERSON CAMILLERI: Thank you.

Would the company like to start?

MERCK PHARMACEUTICALS PRESENTATION

INTRODUCTION

DR. ERB: Good morning, Mr. Chairman, members of the advisory committee, FDA, and ladies and gentlemen. My name is Dennis Erb from the Department of Regulatory Affairs at Merck Research Laboratories. I am pleased to be here today to discuss EMEND, Merck's trade name for aprepitant, for the prevention of chemotherapy-induced nausea and vomiting.

I would like to provide a few introductory remarks before we present the results from our development program. Over one million cancer patients receive chemotherapy each year in the United States. Twenty percent are administered highly emetogenic chemotherapy, the vast majority of which will experience an emetic episode in the absence of antiemetic prophylaxis.

Patients consistently report that nausea and vomiting are among the most distressing side effects of chemotherapy. The disruptive effects of these symptoms on patients' daily lives has been well-documented to the extent that patients may delay potential curative therapy because of these symptoms.

No single class of drugs is fully

effective in preventing chemotherapy-induced nausea and vomiting. Current therapy guidelines recommend a regimen consisting of a 5-HT_3 receptor antagonist plus a corticosteroid. Despite this use, greater than 50 percent of patients still experience nausea and vomiting.

Even with the advent of the 5-HT_3 receptor antagonist, delayed emesis remains a serious problem with patients experiencing symptoms that often last for several days following their chemotherapy.

In light of the need for routine emetogenic use of chemotherapy, effective prevention of nausea and vomiting remains an important goal of health care providers and their patients. Thus, there is a need for new therapies which can improve prevention of nausea and vomiting and provide protection that lasts for several days.

EMEND represents the first new approach in over a decade to address the significant unmet medical need. It has a novel mechanism of action by blocking substance P at the Neurokinin-1 receptor in the brain.

It has a distinct efficacy profile,

providing protection throughout the period when symptoms may occur, both in the acute and in the delayed phases.

EMEND also improves the effectiveness of current therapies, resulting in fewer patients experiencing acute or delayed symptoms. Thus, the potential exists to alter an enduring perception of cancer chemotherapy. Nausea and vomiting need not be inevitable.

As you have seen in the advisory committee briefing document and will hear about today, the development program for EMEND provides compelling evidence to support the use of EMEND in the prevention of chemotherapy-induced nausea and vomiting. Results from the clinical program show that a regimen of EMEND given concomitantly with standard therapy is effective in preventing nausea and vomiting due to highly emetogenic chemotherapy.

Efficacy was superior to that observed with standard therapy alone with significant benefit in both the acute and delayed phases. This advantage was maintained in subsequent cycles of chemotherapy.

Additionally, this regimen was also effective in reducing the impact of these symptoms on patients' daily lives. EMEND when added to standard therapy also demonstrated a favorable safety profile that was similar to standard therapy alone and has a drug interaction profile that is well-characterized.

The presentation today will focus on the data supporting our new drug application for the following indication. EMEND in combination with other antiemetic agents is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

In addition to our speakers, Merck has brought several consultants to the meeting today. So they are available as a resource to the advisory committee during discussions and deliberations.

Our pharmacology consultants with us today are Dr. Paul Andrews, the St. George's Hospital and Medical School; Dr. Merrill Egorin of the University of Pittsburgh Cancer Institute; and Dr. Malcolm Rowland from the University of Manchester.

Our statistical consultant, unfortunately, could not be with us today because of a family emergency. Our clinical consultants include Dr. Ronald De Wit of the Rotterdam Cancer Institute; Dr. Steven Grunberg of the University of Vermont; Dr. Paul *Hesketh from Tufts University School of Medicine; and Dr. Loren Laine from the University of Southern California.

The advisory committee members have previously received a briefing document from Merck that provides more detailed information than time allows us to present this morning.

The outline for today's presentation is as follows. First, Dr. Petty will provide background and rationale for the use of Neurokinin-1 receptors, antagonists for the prevention of chemotherapy-induced nausea and vomiting as well as review the clinical pharmacology data from our program.

Dr. Horgan will present the clinical efficacy information that supports the use of EMEND in preventing nausea and vomiting due to highly emetogenic chemotherapy.

Following Dr. Horgan's presentation, Dr. Reines will present the safety findings from our development program and will summarize the evidence demonstrating that EMEND represents a major advance in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy.

I would now like to turn the podium over to Dr. Petty from the Department of Clinical Pharmacology.

BACKGROUND AND RATIONALE AND CLINICAL PHARMACOLOGY

DR. PETTY: Good morning. This morning I will provide an overview of the pharmacological properties of aprepitant. The key points are summarized on this slide. I will first present data showing that aprepitant has a novel antiemetic mechanism of action relative to currently available antiemetic therapy in that it blocks substance P action via NK_1 receptors in the brain. In both animals and humans, unlike available therapies, it is effective in preventing both acute and delayed chemotherapy-inducted emesis.

Aprepitant has a favorable pharmacokinetic profile that supports once daily oral dosing and requires no dose adjustment in special populations, such as the elderly and patients with renal or hepatic insufficiency.

The background package provides a comprehensive description of the pharmacokinetics and biopharmaceutics of aprepitant. It describes several drug interaction studies with aprepitant that were conducted during the course of this development program. However, several of those studies were conducted to support the use of aprepitant for chronic dosing indications. And due to differences in dose levels or duration of a dosing of aprepitant, they're not relevant to the short-term dosing proposed for prevention of chemotherapy-induced nausea and vomiting.

The studies relevant to administration of aprepitant for the proposed indication will be presented here. And they indicate that drug interactions with the aprepitant regimen for CINV are generally modest and not clinically important. Of

particular importance is that aprepitant has a low potential for interaction with chemotherapy, with which it would be co-administered.

This presentation will first provide a brief overview of the mechanisms of chemotherapy-induced nausea and vomiting. Next, the pharmacological properties of aprepitant and its efficacy in nonclinical models of chemotherapy-induced emesis will be presented.

Finally, I will review the clinical pharmacokinetics of aprepitant, which will include a description of relevant drug interaction studies that were performed.

To place the novel mechanism of action of aprepitant in context, I will provide a brief overview of the mechanisms of chemotherapy-induced nausea and vomiting. There are both central and peripheral mechanisms that contribute to the emetic reflex.

The peripheral component involves effects of chemotherapy within the gut, in which chemotherapeutic agents cause enterochromaffin cells to release serotonin. Acting locally, serotonin

stimulates vagal afferent nerves via 5-HT_3 receptors.

It is at this level that 5-HT_3 antagonists primarily exert their antiemetic effect. These afferents feed into the brain stem, triggering emesis via activation of brain stem loci that control the emetic reflex.

The central component of CINV involves direct stimulation by chemotherapy of these brain stem loci. Within the brain stem, substance P facilitates the emetic reflex by activation of NK_1 receptors. It is at this level that NK_1 antagonists, such as aprepitant, exert their antiemetic effects.

Before describing the antiemetic efficacy of aprepitant in animal models, I will summarize some of the pharmacological properties of aprepitant. The properties of aprepitant can be summarized as follows. First, there's an antagonist for the substance P or NK_1 receptor. Second, it binds specifically and with high affinity to human NK_1 receptors. It is greater than *8,000-fold selective for NK_1 receptors over other receptors that mediate antiemetic activity, specifically dopamine D_2, serotonin 5-HT_3,

corticosteroid, and opiate receptors.

Animal toxicology studies revealed no findings that preclude use of aprepitant in humans.

In the next few slides, I will present data that clearly demonstrate the antiemetic effect of aprepitant on cisplatin-induced emesis in ferrets, a well-established model that is used to assess antiemetic efficacy of various compounds.

The ferret models show pathophysiology of chemotherapy-induced emesis that is similar to humans. These models were used in the discovery of the antiemetic effects of 5-HT_3 receptor antagonists. Since nausea cannot be readily assessed in ferrets, the term "chemotherapy-induced emesis" is used, as opposed to "chemotherapy-induced nausea and vomiting" in humans.

The ferret model has been used to characterize compounds or interventions that induce emesis by either central or peripheral mechanisms. This slide lists various emetogens according to the primary site of action, either central or peripheral, and qualitatively summarizes the effects of either NK_1

or 5-HT_3 antagonists.

In these models, NK_1 antagonists, such as aprepitant, are effective against a broad spectrum of both central and peripheral emetogens; whereas, 5-HT_3 antagonists show a more limited spectrum of activity with efficacy mostly for emetogens that exert their effects via peripheral sites of action.

Among these emetogens, cisplatin is one of the most highly emetogenic agents known. And it exerts its effect by both central and peripheral pathways. Thus, cisplatin-induced emesis in ferrets has often been used to characterize the efficacy of various compounds against highly emetogenic chemotherapy.

In this model, ferrets were given a single intraperitoneal dose of cisplatin at zero hour. And emesis was quantified over the subsequent 72 hours. Vehicle-treated animals, shown in this graph, display the typical biphasic emetic response to chemotherapy with an acute phase from 0 to 24 hours followed by a delayed phase beyond 24 hours.

Aprepitant given orally once daily at a

dose of one milligram per kilogram provided significant efficacy in both the acute and delayed phases of emesis in this model, which was dose-dependent, as shown by an even greater effect at a dose of two milligrams per kilogram. These results demonstrate that aprepitant with once daily oral dosing provides significant protection against both acute and delayed cisplatin-induced emesis in ferrets.

In other ferret experiments that I will not show here but are described in your background package, it was confirmed that the antiemetic effect of aprepitant required central NK_1 receptor antagonism and that aprepitant demonstrates additive efficacy with established antiemetic agents, specifically dexamethasone or a 5-HT_3 receptor antagonist.

To summarize its nonclinical efficacy, aprepitant is active against both the acute and delayed phases of cisplatin-induced emesis. And efficacy was observed with once daily oral dosing.

In the remainder of this portion of the presentation, I will focus on the human pharmacology of aprepitant. Clinical pharmacology studies show

that once daily oral dosing provides acceptable plasma concentrations of aprepitant in humans, which I will show on a subsequent slide.

The pharmacokinetics of aprepitant are not significantly affected by age, gender, race, or body weight. And dose adjustment is not necessary in patients with renal insufficiency or mild to moderate hepatic insufficiency. As I will show subsequently, aprepitant is brain-penetrant and binds to NK_1 receptors in the brain.

Shown here is the plasma concentration profile of aprepitant in healthy subjects, who receive the aprepitant CINV regimen 125-milligram loading dose on day one. Following the day two dose of 80 milligrams, the trough concentration was similar to that following the day one dose. And the plasma concentration of aprepitant after the last dose of 80 milligrams on day three was similar to that on day one.

These data show that the aprepitant three-day regimen provides consistent daily plasma exposure of aprepitant. During the development

program, a five-day regimen was also studied in which the 80-milligram doses were additionally administered on days four and five. The five-day regimen also provided consistent daily plasma concentrations of *aprepitant.

Since aprepitant exerts its effect in the brain, it was important to determine if aprepitant reaches its intended target in humans. This was accomplished using positron emission tomography, or PET.

Displayed in the next few slides are the results of PET studies conducted with aprepitant. For these studies, a specific NK_1 receptor binding tracer was developed. And the binding of the tracer in a human brain is displayed in this PET scan. Note that with this color scale, the blue color represents low binding of the tracer; whereas, red represents the highest level of binding to NK_1 receptors. These red areas correspond to the corpus striatum, an area known to have a high concentration of NK_1 receptors.

When aprepitant was administered for two weeks to healthy volunteers, as you can see in the

lower PET scan, there was a high level of blockade of brain NK_1 receptors after aprepitant dosing.

This graph displays the relationship between aprepitant plasma concentration and brain NK_1 receptor occupancy determined approximately 24 hours after the last dose of aprepitant. Each point represents the result from an individual subject. Note that as plasma concentrations increase, there is an expected increase in the level of brain NK_1 brain receptor blockade.

Superimposed here is a crosshatched area that represents the mean with standard deviation of plasma trough concentrations of aprepitant that are achieved with the three-day CINV regimen. Thus, this regimen is anticipated to provide a high level of blockade of brain NK_1 receptors.

In the remainder of my presentation, I will provide an overview of potential drug interactions with aprepitant. As I mentioned previously, the potential for drug interactions with aprepitant was well-characterized in several clinical drug interaction studies, all of which are described

in your background package.

Studies utilizing the regimen for CINV, which I will describe here, showed that the aprepitant regimen for CINV generally has at most modest drug interaction effects and that it has low potential for interaction with chemotherapy.

In vitro experiments indicated that aprepitant is metabolized by cytochrome P450 3A4, an enzyme that metabolizes more than half of all drugs. Thus, it was anticipated that drugs that induce or inhibit CYP3A4 activity would affect the pharmacokinetics of aprepitant. And this was confirmed in clinical studies that I will not discuss here but are described in your background package.

In vitro data also indicated that aprepitant inhibited CYP3A4 activity, raising the possibility that it might affect other drugs metabolized by CYP3A4. Therefore, it was important to characterize the potential for aprepitant to inhibit CYP3A4 *in vivo*.

Orally administered midazolam is a well-characterized sensitive probe used to assess the

effects of drugs on CYP3A4 activity *in vivo*. It is possible to rank the inhibitory effects of CYP3A4 of various drugs by their ability to increase plasma concentrations of midazolam defined as the fold increase in midazolam in plasma AUC.

This slide shows a scale of strength of CYP3A4 inhibition going from weak on the left to strong on the right. On this scale, ketoconazole, one of the strongest CYP3A4 inhibitors known, produces a 16-fold increase in midazolam AUC. Generally, a two to five-fold increase is considered moderate inhibition and less than two-fold increase is weak inhibition. Other strong inhibitors are itraconazole and clarithromycin.

Agents considered moderate inhibitors include erythromycin, the calcium channel blocker diltiazem, and verapamil, and grapefruit juice. The aprepitant five-day regimen for CINV on both the first and last day of dosing results in no more than moderate CYP3A4 inhibition. And, thus, it produces CYP3A4 inhibition comparable to grapefruit juice and widely used drugs, such as diltiazem and verapamil.

Although this degree of inhibition of CYP3A4 would not be expected to produce clinically important interactions with most drugs, it was important to characterize potential interactions of aprepitant with drugs with which it might be frequently co-administered. This includes other antiemetics, such as the corticosteroids dexamethasone and methylprednisolone as well as the 5-HT_3* antagonists ondansetron and granisetron. Note that all of these agents are metabolized to some extent by CYP3A4.

Also investigated was the potential for aprepitant to affect the pharmacokinetics of drugs with narrow therapeutic indices, including docetaxel, a chemotherapeutic agent metabolized by CYP3A4; digoxin; and warfarin.

Note that digoxin is a drug whose pharmacokinetics are dependent on P-glycoprotein, a membrane-bound transporter that also plays a key role in the disposition of many chemotherapeutic agents.

Thus, evaluation of the potential effects of aprepitant on the pharmacokinetic of docetaxel and

digoxin provides a reasonable assessment of its potential to affect the pharmacokinetics of several chemotherapeutic agents whose clearance is dependent on CYP3A4 or P-glycoprotein.

Described first is the effect of aprepitant on dexamethasone, which was the corticosteroid used in Phase III studies. Shown here are plasma concentrations of dexamethasone in healthy subjects on day one of a five-day regimen in which a 20-milligram dose of dexamethasone was orally co-administered with or without a 125-milligram dose of aprepitant. Co-administration of aprepitant resulted in an approximate two-fold increase in the dexamethasone AUC.

On day five of the five-day regimen, which included oral doses of eight milligrams per day of dexamethasone and 80 milligrams per day of aprepitant.

There was also an approximate two-fold increase in dexamethasone AUC when co-administered with aprepitant. This effect of aprepitant on dexamethasone served as the basis for reduction of the dexamethasone doses in the aprepitant treatment arms

in Phase III studies. This provided balanced exposure of dexamethasone in the two treatment arms, which enabled evaluation of antiemetic efficacy, not confounded by variable dexamethasone exposure.

Methylprednisolone is also used frequently in antiemetic regimens and is metabolized by CYP3A4. In this study, it was of interest to evaluate the effect of aprepitant on IV-administered methylprednisolone since this route of administration is used frequently. Here methylprednisolone was administered as a 125-milligram IV dose with and without the 125-milligram loading dose of aprepitant.

The results showed a small, approximately 34 percent, increase in methylprednisolone AUC. This indicates that aprepitant had a weak inhibitory effect on IV-administered methylprednisolone. A minimal effect of aprepitant on another IV-administered CYP3A4 substrate was demonstrated in a study using IV ondansetron.

Ondansetron is the 5-HT_3 antagonist that was used in Phase III studies. In this study ondansetron was co-administered to healthy subjects at

the same dose used in the Phase III studies, as a 32-milligram IV dose on day one with a 375-milligram dose of aprepitant, which is three-fold higher than the aprepitant dose used in Phase III studies. As shown here, there was little effect of aprepitant on plasma concentrations of ondansetron .

Granisetron is a 5-HT_3 antagonist also used in the treatment of CINV and is metabolized by CYP3A4. Since this drug might be co-administered with aprepitant to prevent CINV, a separate study was conducted in which granisetron was administered at a dose of 2 milligrams orally with a 125-milligram dose of aprepitant on day one.

As shown by the granisetron plasma concentrations in the right graph, there was no significant effect of aprepitant on granisetron pharmacokinetics. From these studies, it is concluded that no dose adjustments of ondansetron or granisetron are required when co-administered with aprepitant. These results also indicated that moderate inhibition of CYP3A4 by aprepitant does not translate into significant pharmacokinetic effects for some orally

administered CYP3A4 substrates, such as granisetron.

As mentioned previously, chemotherapeutic agents with narrow therapeutic index drugs and, thus, pharmacokinetic interactions with these drugs could substantially alter their toxicities.

Cisplatin, which was used in the Phase III studies, is not metabolized by CYP3A4 or other CYPs. The pharmacokinetics of cisplatin are unlikely to be affected by aprepitant since data indicate that the potential for aprepitant to interact with chemotherapeutic agents would be via CYP3A4. Since many chemotherapeutic agents are metabolized by CYP3A4*, it is important to evaluate the potential effects of aprepitant on a CYP3A4-metabolized chemotherapeutic agent, specifically docetaxel.

In addition, the pharmacokinetics of several chemotherapeutic agents are modulated by P-glycoprotein. Thus, it was also important to evaluate potential effects of aprepitant on P-glycoprotein activity using digoxin, which is a P-glycoprotein substrate.

Finally, warfarin is occasionally

administered to cancer patients receiving chemotherapy. And, therefore, the effect of aprepitant on warfarin pharmacokinetics was evaluated.

Docetaxel is an appropriate agent to assess the potential for aprepitant to affect the pharmacokinetics of chemotherapeutic agents because it is metabolized predominantly by CYP3A4 and it is also a P-glycoprotein substrate.

In this particular study, which is ongoing, patients receive the same IV dose of docetaxel in each of two consecutive cycles given at least three weeks apart. The pharmacokinetics of docetaxel are assessed in each cycle.

In one of the two cycles, the patients also receive the aprepitant regimen for CINV in which the first dose of aprepitant is given one hour prior to docetaxel infusion. In the other cycle, patients do not receive aprepitant.

This slide summarizes the data from the first five patients who have completed the study. Shown on the left is a plot of the mean plasma concentration profiles of docetaxel with and without

aprepitant. And on the right are the docetaxel AUC values for each patient in both treatment cycles.

Note that these curves are virtually superimposable and that the individual AUC values are similar between treatment periods for each patient. This indicates that there was little, if any, effect of aprepitant on docetaxel pharmacokinetics in these five patients.

To assess the potential for aprepitant to affect P-glycoprotein, healthy subjects were doses to steady state with digoxin and were then administered the aprepitant five-day regimen for CINV.

Shown here are plasma concentrations of digoxin with and without aprepitant on the first day of the CINV regimen. There was no significant effect of aprepitant on digoxin pharmacokinetics on day one or at any other time point examined. It is concluded that no clinically meaningful interactions with P-glycoprotein substrates are expected with the aprepitant regimen and that no dose adjustment of digoxin is required when it is co-administered with aprepitant.

To summarize, the potential for aprepitant to affect the pharmacokinetics of chemotherapeutic agents, it has been demonstrated that CYP3A4 and P-glycoprotein are common pathways that affect the pharmacokinetics of chemotherapeutic agents.

We have demonstrated that there is weak to no effect of aprepitant on IV-administered CYP3A4 substrates, including methylprednisolone, ondansetron, and the chemotherapeutic agent docetaxel. We have also demonstrated that there is no effect of aprepitant on a P-glycoprotein substrate.

Therefore, we conclude that aprepitant has low potential to produce clinically meaningful effects on the pharmacokinetics of IV chemotherapeutic agents. This conclusion is supported by safety data from the Phase III studies that will be presented by Dr. Reines.

To evaluate the effect of aprepitant on warfarin, a study was conducted in which healthy subjects were titrated to constant low doses of warfarin followed by administration of either the aprepitant three-day regimen for CINV or placebo.

Shown here are the ratios of changes from baseline in trough plasma concentrations of the two warfarin isomers: R warfarin and S warfarin. These were measured during and for several days after administration of aprepitant. And they reflect the effect of aprepitant relative to placebo. There was a modest 34 percent reduction in S warfarin concentrations five days after completion of the regimen with no meaningful effect on R warfarin.

The decrease in S warfarin, which is metabolized by CYP2C9, was accompanied by a small decrease in the international normalized ratio of the prothrombin time, or INR. This is consistent with modest induction by aprepitant of CYP2C9 activity, which was confirmed in a separate study using tolbutamide as a CYP2C9 probe substrate. In that study, which is not shown here, a modest CYP2C9 induction was returning to baseline by day 15, which is one week beyond the last time point shown on this slide. This small inductive effect on warfarin warrants closer monitoring of the INR in patients taking warfarin.

In summary, aprepitant has a novel antiemetic mechanism of action relative to currently available antiemetic therapy by blocking substance P action via NK_1 receptors in the brain. It is effective in preventing both acute and delayed chemotherapy-induced emesis in ferrets.

Aprepitant has a favorable pharmacokinetic profile that supports once daily oral dosing and requires no dose adjustment in special populations, such as the elderly and patients with renal or hepatic insufficiency.

The potential for drug interactions with aprepitant has been well-characterized. And drug interactions with the aprepitant regimen for CINV are generally modest and not of clinical significance for most drugs with which it would be co-administered.

Pharmacokinetic data as well as safety data from the clinical studies in patients receiving chemotherapy indicate that aprepitant has a low potential for interaction with chemotherapy with which it would be co-administered.

In conclusion, the pharmacokinetics of

aprepitant and the potential for clinically meaningful drug interactions with aprepitant have been well-characterized. Appropriate guidance can be provided for safe and effective use in the intended patient population.

I will now turn the podium over to Dr. Horgan, who will present the efficacy data from studies of patients with chemotherapy-induced nausea and vomiting.

Thank you.

CLINICAL EFFICACY

DR. HORGAN: Good morning. Chemotherapy characterized as highly emetogenic evokes symptoms in the vast majority of patients in the absence of preventive therapy.

Current therapy to prevent symptoms consists of a combination of two agents: a 5-HT_3 receptor antagonist and a corticosteroid. Despite this therapy, at least 50 percent of patients still have symptoms of nausea and vomiting when they receive highly emetogenic chemotherapy. Hence, there is an unmet medical need for improved therapy. The clinical

data we will present demonstrates that aprepitant will help meet this medical need.

Nausea and vomiting typically continue for several days following the administration of emetogenic chemotherapy. A convention is involved to delineate the time course of these symptoms. Early symptoms are referred to as acute and later symptoms as delayed. In the literature and in previous antiemetic programs, 24 hours after the administration of chemotherapy has been the transition between the acute and the delayed phases.

All clinical studies that we conducted assessed efficacy in both phases with acute, consistently defined as zero to 24 hours. In more recent studies, particularly Phase III, we emphasized an overall time frame, which is a merger of the acute and delayed phases, because of its greater clinical relevance.

This slide summarizes the basis for current therapy for prevention of symptoms associated with highly emetogenic chemotherapy. 5-HT_3 receptor antagonists prevent symptoms, acute symptoms, in

approximately 50 percent of patients, though they have equivocal efficacy in the prevention of delayed symptoms and are only approved for prevention of acute symptoms.

Corticosteroids augment the acute efficacy of 5-HT_3 receptor antagonists and also have efficacy as monotherapy in the prevention of delayed symptoms. Though corticosteroids are recommended in consensus treatment guidelines by the American Society of Clinical Oncology and are extensively used in clinical practice, they are not approved for use as antiemetics in the United States.

The program objective was to define the potential role of aprepitant in the prevention of nausea and vomiting associated with highly emetogenic chemotherapy. The program followed the development paradigm of agents previously approved for the prevention of the symptoms of chemotherapy-induced nausea and vomiting, notably the 5-HT_3 receptor antagonists.

The program addressed three questions sequentially. The first question, does aprepitant

work alone as an antiemetic, as implied by the preclinical data from the ferret model? A monotherapy study was done to answer this question.

Next we asked, is a regimen containing aprepitant more effective than current standard therapy? Three studies were done to answer this question. We will present data from one of these studies, the one that provided the most pivotal information. The data from the other two studies are in your background.

Our last question was, what was the optimum dose? This was addressed by a single dose-binding study.

Finally, two studies were done to confirm that the Phase III regimen is effective and safe. Before addressing these questions specifically, I am going to spend a few moments providing a framework for understanding the approach we took.

All studies enrolled patients receiving cisplatin. There were several compelling reasons why we focused on this patient population. Cisplatin is a cornerstone of current therapy for common cancers,

such as lung and ovarian. Cisplatin is the most emetogenic chemotherapeutic agent and has a predictable and well-characterized pattern of emesis lasting several days.

A dose of cisplatin greater than or equal to 50 milligrams per meter^2 is regarded as being highly emetogenic. Cisplatin has been the benchmark chemotherapy for evaluation and approval of novel antiemetic agents, notably the 5-HT_3 receptor antagonists ondansetron, granisetron, and dolasetron; and also the dopamine receptor antagonist metoclopramide.

Efficacy in the prevention of nausea and vomiting associated with cisplatin has generally been predictive of efficacy in the prevention of symptoms associated with other chemotherapeutic agents, such as carboplatin, doxorubicin, and cyclophosphamide.

Some important elements of the clinical trials we did included the following. All studies were double blind versus an appropriate control. All patients enrolled were cisplatin-naive.

All patients received high-dose cisplatin

infused over less than three hours on day one. The cisplatin dose for enrollment was greater than 70 milligrams per meter^2 in all studies except the initial study, when it was greater than 50 milligrams per meter^2. Additional chemotherapy was permitted, though additional emetogenic chemotherapy was only allowed on day one.

Randomization was stratified for gender and additional emetogenic chemotherapy. Rescue therapy was allowed to treat established nausea or vomiting.

A daily patient diary was used to collect efficacy data. This included all emetic events, all use of rescue therapy, and nausea assessments. The primary efficacy analyses were focused on the first cycle of chemotherapy and modified intention-to-treat populations.

Several endpoints were assessed in order to comprehensively understand the efficacy profile of aprepitant. The primary endpoint in the majority of the studies and in both Phase III studies was complete response. And the efficacy data in this presentation

emphasize this endpoint.

A patient has a complete response if they have both no emetic episodes and also do not take rescue therapy. Since rescue therapy is permitted for emesis and nausea, this endpoint reflects control of both emesis and nausea.

Complete response was the primary endpoint for the 5-HT_3 receptor antagonists ondansetron and dolasetron, which were both approved for the prevention of chemotherapy-induced nausea and vomiting.

Other endpoints focused on emetic episodes, use of rescue therapy, and the impact of nausea and vomiting on daily life.

And so back to our questions. The first one, does aprepitant work alone as an antiemetic? This question was answered in a monotherapy study which used the intravenous prodrug formulation of aprepitant, as explained in your background.

There were two treatment groups. One received a single dose of aprepitant intravenously and the other a single dose of ondansetron, 32 milligrams,

intravenously. Both aprepitant and ondansetron were administered only on day one prior to the administration of cisplatin.

A placebo-controlled group could not be included for ethical reasons. As based on historical data from the literature, almost all patients receiving this dose of cisplatin will be predicted to have emesis in the absence of therapy.

The data during the acute phase and the delayed phase are shown. The vertical axis shows the percent of patients with a complete response. During the acute phase, both aprepitant and ondansetron had similar efficacy. During the delayed phase, the aprepitant-treated patients had a much better outcome than those treated with ondansetron. Forty-eight percent had a complete response versus 17 percent. And this difference was statistically significant.

To provide context, the dotted lines illustrate the anticipated response in the absence of treatment based on historical data. So this study provided very useful information. It showed that aprepitant is an effective antiemetic clinically

showing both the acute and the delayed phases. It also showed that aprepitant has a distinctive efficacy profile relative to a 5-HT_3 receptor antagonist with significantly superior efficacy in the prevention of delayed symptoms.

The distinctive efficacy profile of aprepitant implied that better efficacy might be obtained by combining it with other antiemetics, such as a 5-HT_3 receptor antagonist. This possibility provided the rationale for the next question we asked. Is a regimen with aprepitant more effective than current standard therapy?

We did three studies to answer this question and will present data from one of these that was particularly helpful in establishing a rationale for subsequent studies in the Phase III regimen. The data from the other two are in your background.

I would like to emphasize some important design features of this study. An aprepitant loading dose strategy was used with a tablet formulation.

Patients received aprepitant, 400 milligrams, on day one. And if treated on subsequent

days, they received 300 milligrams of aprepitant daily. This day one loading dose was particularly high relative to the day one dose ultimately selected for Phase III.

The control group received a regimen that was consistent with standard clinical practice at the time of the initiation of the study. This control regimen consisted of therapy on day one only with both a single dose of a representative 5-HT_3 receptor antagonist, granisetron, and a single dose of a corticosteroid. Granisetron was administered intravenously and dexamethasone orally.

The design of the study is shown, the control regimen granisetron and dexamethasone on day one only, placebo for aprepitant on day one and days two to five. Patients in the other two treatment groups also received the components of the control regimen on day one with the addition of aprepitant, 400 milligrams, on day one in both. One group received aprepitant on day one only. The other group received aprepitant on day one and also on days two to five.

In summary, three treatment groups, the control group receiving standard therapy, one day aprepitant regimen, and a five-day aprepitant regimen.

The data during the acute and delayed phases are shown. The vertical axis again shows the percentage of patients with a complete response. During the acute phase, both aprepitant treatment groups were significantly more effective than the control group. During the delayed phase, both aprepitant treatment groups were also significantly more effective than the control regimen. Also, the five-day aprepitant regimen was numerically more effective than the one-day regimen in the prevention of delayed symptoms.

We concluded that aprepitant enhances the efficacy of a standard therapy regimen during both the acute and delayed phases. We also concluded that aprepitant is more effective when administered for multiple days in the prevention of delayed symptoms, even when a very high dose of aprepitant, 400 milligrams, is administered on day one.

Hinting that continued dosing is more

effective in the prevention of delayed symptoms was also shown in the second study, the details of which are in your background.

Based on these conclusions and the data from the other studies that evaluated different aprepitant regimens presented in your background, we then did a dose finding study.

There were several noteworthy design features of this study. The primary hypothesis related to overall prevention of symptoms, "overall" meaning the entire five days following the initiation of cisplatin therapy. As mentioned before, the overall phase is affusion of the acute and delayed phases and is favored because it is the most clinically relevant time frame for the primary assessment of efficacy.

The control group received a standard therapy regimen that consisted of therapy on day one with both a 5-HT_3 receptor antagonist and a corticosteroid followed by continued therapy with a corticosteroid, dexamethasone, on subsequent days.

Instead of chronicitron, a study

previously, the 5-HT_3 receptor antagonist selected was ondansetron. Based on the very similar efficacy profiles of the various 5-HT_3 receptor antagonists, this change was not predicted to significantly alter the efficacy profile of the aprepitant regimen.

There was a transition to an aprepitant capsule formulation with improved bioavailability. The aprepitant capsule was used in all subsequent studies and is the formulation proposed for market.

The dose finding study was initiated with two aprepitant regimens. The first was 375 milligrams on day one followed by 250 milligrams on days 2 to 5. The second was 125 milligrams on day one followed by 80 milligrams on days 2 to 5.

After initiation of the study, new data became available which demonstrated that the aprepitant capsule formulation had even better bioavailability than anticipated.

As a result of this new information, it was predicted that both aprepitant regimens would have similar clinical efficacy. So in light of this, in order to adequately explore the aprepitant dose

response, the study was modified.

The 375/250 milligram regimen was discontinued after enrollment of 35 patients. The study was then resumed with a new allocation schedule and new drug supplies and the addition of a 40/25 milligram aprepitant regimen. This slide shows the design of the second part of the study after the modification of the aprepitant treatment groups.

The control regimen received ondansetron, the control standard therapy regimen, ondansetron and dexamethasone on day one followed by dexamethasone on days two to five. Patients in the other two treatment groups received this standard therapy regimen, and both also received a five-day aprepitant regimen. The first was aprepitant, 40 milligrams, on day one followed by 25 milligrams on days 2 to 5. And the other was 125 milligrams on day one followed by 80 milligrams on subsequent days. The objective of the study was to assess the aprepitant dose response.

The data for the primary hypothesis overall complete response are shown. The vertical axis shows the percentage of patients with a complete

response. Both aprepitant regimens were significantly more effective than the control regimen.

A formal dose response analysis was done, which demonstrated that the 125/80 milligram regimen was significantly superior to the 40/25 milligram regimen. The data during the acute phase and the delayed phase are shown separately. The 125/80 milligram aprepitant regimen was significantly more effective than the control regimen during both the acute and the delayed phase; whereas, the 40/25 milligram aprepitant treatment regimen was significantly more effective than the control regimen during the delayed phase only.

This Kaplan-Meier curve illustrates the time to first emetic episode or rescue over the five-day evaluation period for the control group. The horizontal axis shows time over the evaluation period of 120 hours. The vertical axis, truncated at 40 percent, shows the percentage of patients with no emesis or rescue. At time zero, the time of initiation of cisplatin, 100 percent of the patients have had no emetic episodes and have not taken rescue.

At 120 hours, less than 50 percent of patients in the control group have had no emetic episodes and have not taken rescue.

Few patients are having more emesis or are taking rescue in the first few hours. However, after approximately 18 hours, a substantial portion of the patients are having symptoms. Initial emetic episodes and use of rescue are concentrated in the first 72 hours.

The benefit of addition of both dose regimens of aprepitant is clearly seen with the 125/80 milligram regimen superior to the 40/25 milligram regimen.

Initial emetic episodes and use of rescue are also concentrated within the first 72 hours with the addition of aprepitant. This display shows the data from the 375/250 milligram regimen superimposed. As predicted, the outcome in the patients in the 375/250 milligram regimen and the 125/80 milligram regimen was very similar.

The conclusions from the dose finding study were that the aprepitant 125/80 milligram

regimen is effective. The 40/25 milligram aprepitant regimen was less effective. And the 375/250 milligram aprepitant regimen added little or no benefit relative to the 125/80 milligram regimen.

Almost all initial therapy failures occurred within 72 hours, implying that 3-day dosing with aprepitant would provide full benefit. Based on these conclusions, we proceeded to Phase III in order to confirm the effectiveness and safety of a 3-day aprepitant regimen, 125 milligrams administered on day one followed by 80 milligrams administered on days 2 and 3.

The Phase III hypothesis was compared to standard therapy, the aprepitant regimen will provide superior control of nausea and vomiting as measured by the proportion of patients with an overall complete response. That is, no emesis and no rescue in the 120 hours following the initiation of cisplatin.

In order to rigorously assess this hypothesis, two Phase III multinational studies were done with multiple-cycle extensions. These studies enrolled over 1,000 patients and were 2 of the largest

antiemetic trials with multiple-cycle extensions ever done in this patient population: cancer patients treated with high-dose cisplatin.

The aprepitant regimen was refined for Phase III. Aprepitant was dosed for three days, as I mentioned previously. The dexamethasone dose was reduced in the aprepitant treatment group. So the plasma dexamethasone levels would be similar in both treatment groups.

The Phase III study design. Two treatment groups; the control therapy regimen, ondansetron and dexamethasone on day one followed by dexamethasone on days two to four.

Patients in the aprepitant treatment group received this standard therapy regimen with the refinement that the dexamethasone dose was reduced relative to the control group. On day one, the control group received 20 milligrams dexamethasone; whereas, the aprepitant group received 12 milligrams. On days two to four, the control group received 16 milligrams of dexamethasone daily; whereas, the aprepitant group received 8 milligrams daily.

The key inclusion criteria were administration of high-dose cisplatin, greater than 70 milligrams per meter^2 on day one. Exclusion criteria included significant elevations of liver function tests, AST, ALT, and bilirubin, reduced renal function, and reduced neutrophil and white blood cell counts, as shown. The concomitant or very recent use of strong CYP3A4 inhibitors or CYP3A4 inducers were also precluded.

The treatment groups were similar in terms of gender, age, and additional emetogenic chemotherapy, as seen in the data combined from both studies. These are all risk factors for the development of nausea and vomiting.

The primary cancer diagnoses were similarly distributed between the treatment groups, data combined from both studies. The vast majority of patients in the studies, around 95 percent, received concomitant chemotherapy in addition to cisplatin.

The frequency of concomitant therapy with specific chemotherapeutic agents was similar in both treatment groups. The efficacy data for the primary

endpoint of overall complete response are shown for the first Phase III study, protocol 052.

Fifty-two percent of the patients in the control group had a complete response versus 73 percent in the aprepitant group, an increment of 21 percentage points, which was highly significant, *p* less than .001.

The outcome in the second Phase III study, protocol 054, was strikingly similar. Forty-three percent of patients had a complete response in the control group versus 63 percent in the aprepitant group, an increment of 20 percentage points, which was also highly significant, *p* less than .001.

Thus, the primary analysis in both studies showed a consistent advantage for the aprepitant regimen in the overall prevention of nausea and vomiting associated with highly emetogenic chemotherapy, which was highly significant.

The efficacy data for the key secondary endpoints of complete response during the acute and delayed phases in both of the Phase III studies are shown. Both studies showed a consistent advantage for

the patients treated with the aprepitant regimen during both the acute and the delayed phases when analyzed separately. The differences were also of similar significance in both studies with *p* values consistently less than .001.

These Kaplan-Meier curves illustrate the time to first emetic episode or rescue for the treatment groups over the five-day evaluation period in both Phase III studies. The advantage provided by the addition of aprepitant throughout the acute and delayed phases was clearly replicated in both studies and was statistically significant.

The efficacy data for the endpoints of no emesis and no rescue overall are shown for both studies. These endpoints are the individual components of the primary endpoint of complete response.

Both studies show a consistent advantage for the patients treated with the aprepitant regimen for both the no emesis and no use of rescue therapy endpoints. The efficacy of the aprepitant regimen is, thus, supported by both components of the primary

endpoint. The greater use of rescue therapy in the control group is particularly important to bear in mind in the context of the assessment of the control of nausea, which I will now discuss.

Nausea is a particularly important symptom for patients, which frequently occurs in conjunction with vomiting. Though our primarily assessment of the efficacy of aprepitant was in the prevention of the syndrome of chemotherapy-induced nausea and vomiting, we also carefully assess nausea prevention independently.

The assessment of nausea is more complex than either the assessment of emetic events or use of rescue therapy because of its subjective nature. Nausea was assessed daily by patients using a validated 100-millimeter visual analog scale. The scale was anchored by zero millimeters representing no nausea and 100 millimeters representing nausea as bad as it could be.

Patients placed a vertical mark daily on the scale corresponding to their level of nausea in response to the diary question, "How much nausea have

you had over the past 24 hours?"

Two pre-specified nausea endpoints were analyzed with data from the daily visual analog scale readings: no nausea and no significant nausea. No nausea was defined as a maximum rating of less than five millimeters on each day during the overall five-day assessment period.

This definition of no nausea was also used by the most recently approved $5\text{-}HT_3$ receptor antagonist, dolasetron. No significant nausea was defined as a maximum rating of less than 25 millimeters each* day during the overall 5-day assessment period. This definition of no significant nausea correlates with nausea that does not interfere with daily activities. The efficacy data for the pre-specified secondary endpoints of no nausea and no significant nausea are shown for both studies.

Both studies showed a consistent numerical advantage for the aprepitant regimen for both nausea endpoints, though, as I mentioned before, it is important to bear in mind that rescue therapy was most frequently used in the control group.

Statistical significance was achieved for the no nausea endpoint in protocol 054. To explore further the control of nausea, the data from both studies were merged in post hoc analyses of both nausea endpoints and are shown.

Statistically significant advantages for the aprepitant-treated patients for both endpoints were seen in these merged post hoc analyses. These data show that the addition of aprepitant consistently improves the control of nausea associated with highly emetogenic chemotherapy.

Other pre-specified endpoints were also studied. These included the composite endpoints, complete protection, and total control. Complete protection is defined as complete responses plus no significant nausea; that is, no emesis, no rescue, plus no significant nausea.

Aprepitant was significantly superior to control in both Phase III studies in terms of complete protection. And the data is in your background. Total control is defined as complete responses plus no nausea; that is, no emesis, no rescue, plus no

significant nausea.

Aprepitant was significantly superior to control in protocol 054 in terms of total control and numerically better in protocol 052. The data for total control are in your background.

Symptom relief alone may not fully describe the benefits of effective antiemetic therapy to patients because it does not assess the impact of nausea and vomiting on patients' daily lives. So we assessed the impact of nausea and vomiting on daily life using a validated nausea and vomiting-specified questionnaire.

The questionnaire has two domains: an emesis-specific domain and a nausea-specific domain. Using the overall score derived from the questionnaire is a pre-specified analysis, aprepitant was significantly superior to control in both Phase III studies in terms of impact on daily life, as detailed in your background.

The data derived from the individual emesis and nausea domains, which are not present in your background, were also supportive of aprepitant's

benefit to patients. In order to assess the benefit of aprepitant in patients receiving a particular emetic regimen, we did a post hoc efficacy analysis in the subset of patients treated with both cisplatin and additional emetogenic chemotherapy, specifically cyclophosphamide and/or doxorubicin.

Predictably, the complete response was very low in the control group because of the more intense emetic stimulus, only 26 percent of patients having a complete response. The advantage provided by addition of aprepitant was 33 percentage points, more than twice the response in the control group, and a very substantial therapeutic effect in these patients that was highly significant.

I would like to briefly summarize the aprepitant cycle 1 efficacy data. The aprepitant regimen was effective in two replicate clinical trials. Overall, 20 percent fewer patients vomited or required rescue medications for established nausea or emesis, a *p* less than .001, in both studies.

The superiority of aprepitant was evident in both the acute and delayed phases for both

components of the primary endpoint: emesis and the use of rescue medications. The superiority of aprepitant was also evident in patients taking cisplatin plus other emetogenic chemotherapy. There was a consistent advantage to the aprepitant regimen on both nausea endpoints, and it's important to bear in mind in considering the nausea data that more rescue medications were used in the control group in both *studies.

All of the efficacy data we have presented has related to cycle 1 of chemotherapy. Since cancer patients typically receive multiple cycles of chemotherapy treatment, the assessment of antiemetic efficacy during those multiple cycles is important.

The vast majority of antiemetic studies have only collected cycle 1 data. And those that have collected multiple-cycle data have frequently been open label studies.

The interpretation of data from multiple-cycle extensions is complicated because of the high attrition rate in this patient population and the potential for bias when observing a subset of the

cycle 1 patients. Both Phase III studies incorporated multiple-cycle extensions.

Patients could receive the same blinded therapy they received in cycle 1 in up to five additional cycles. Sixty-eight out of 71 study sites participated in the optional multiple-cycle extension.

Data collection was streamlined, and patients were simply asked to provide "Yes" or "No" responses to two questions posed at the day six to eight clinic visit, "Have you had any episodes of vomiting or retching since your chemotherapy started in this cycle?" and "Have you had any nausea since your chemotherapy started in this cycle that interfered with normal daily life?"

The observed proportion of patients without emesis and significant nausea are shown during each of the multiple cycles two to six. Data was combined from both Phase III studies. A consistent advantage is seen for the patients receiving the aprepitant regimen, which appears to be maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Another way to evaluate the multiple-cycle data is the time to first emesis and the time to first significant nausea during the extensions. Data from both studies are combined and are shown using a Kaplan-Meier approach.

A consistent advantage for the patients receiving the aprepitant regimen in terms of emesis-free time and significant nausea-free time appears to be maintained throughout repeat cycles for those patients continuing in the extension, though the advantage is not as pronounced for the no significant nausea endpoint compared to the no emesis endpoint.

In summary, we performed two large Phase III studies to demonstrate that the addition of aprepitant to a regimen of a 5-HT_3 receptor antagonist and a corticosteroid is beneficial in the prevention of nausea and vomiting due to highly emetogenic chemotherapy.

The benefit is clinically important, is evident during both the acute and the delayed phases, and appears to be sustained during multiple cycles of chemotherapy.

My colleague Dr. Scott Reines will now present the safety profile of receptor antagonist and complete our presentation. Thank you.

CLINICAL SAFETY

DR. REINES: Good morning. I would like to review with you the key safety findings from the aprepitant clinical development program, which included over 3,000 subjects and patients treated with aprepitant. Over 1,400 of these patients received aprepitant for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy.

The background document summarizes the safety of aprepitant across these populations. Of note is the low inherent toxicity of the drug documented in studies in non-cancer patients in which aprepitant, even at very high doses for up to eight weeks, was associated with few adverse events.

My presentation this morning will focus on the safety of aprepitant in the Phase III clinical trials in cancer patients, protocols 052 and 054, which utilize the 3-day antiemetic regimen for which approval is being sought.

Initially I will discuss cycle 1 of chemotherapy and then briefly review safety during administration of aprepitant over multiple chemotherapy cycles.

Based on its pharmacokinetic profile and our previous clinical experience, we predicted that aprepitant would be very well-tolerated in the antiemetic regimen host for marketing. The Phase III clinical trials confirm that prediction.

This slide provides an overall summary of clinical adverse experiences during cycle 1 of the Phase III clinical trials. The incidences of all clinical adverse experiences, those defined as drug-related are serious, discontinuations due to clinical adverse experiences, and death, in the aprepitant and control groups are displayed.

The incidences of all categories of adverse experiences are generally similar between the treatment groups with the exception of adverse experiences defined by the investigator as drug-related, which were somewhat more frequent in the aprepitant treatment group. The difference was

primarily attributable to small increases in drug-related hiccups, anesthenia, and fatigue, which were generally mild and trangient.

The incidences of the most common serious clinical adverse experiences in the aprepitant and control groups are displayed in this slide. Of note, the overall incidence of serious clinical adverse experiences during cycle 1 is essentially identical in the two treatment groups, 13.4 versus 13.6 percent. No specific adverse experience occurred in more than 2.2 percent of patients. And the incidences of specific events were similar between groups.

Febrile neutropenia occurred as a serious AE in 1.3 percent of patients in either group. The spectrum of adverse events is typical of cancer patients receiving chemotherapy.

My next slide summarizes the Phase III chemotherapy cycle 1 laboratory adverse experiences. The overall incidences of all laboratory adverse experiences as well as those defined as serious or drug-related and discontinuations due to laboratory adverse experiences were generally similar between the

treatment groups during cycle 1 of the Phase III trials.

When used in clinical practice, aprepitant will be administered with a variety of concomitant therapies. During Phase III, we sought to confirm the prediction based on clinical pharmacology data that aprepitant would not have clinically important interactions with these other medications.

We approached the question in several ways, as illustrated here. Since all patients receive cisplatin, potential renal and neurological effects, which are the dose-limiting toxicities with this agent, were carefully monitored. Cisplatin-induced renal effects were evaluated by analysis of serum creatinine. And particular attention was paid to nervous system and ototoxicity.

Toxicities of other types of chemotherapy, which were frequently administered in addition to cisplatin, were evaluated by changes in neutropenia and other hematological parameters as myelosuppression is the dose-limiting toxicity for the majority of these chemotherapies.

Other common chemotherapy-induced effects include fever, infection febrile neutropenia, and dehydration. These hematological parameters and clinical adverse experiences as well as those indicative of potential glucocorticoid toxicity; that is, hypertension, hyperglycemia, and hypokalemia, were pre-specified as worthy of special attention during Phase III.

In addition, patients receiving chemotherapy metabolized, at least in part, by CYP3A4, the enzyme responsible for aprepitant metabolism, were identified and evaluated, both as part of the entire patient cohort and as separate subgroups.

Before discussing the data on this slide, I would like to describe the way we collected and evaluated adverse laboratory findings during Phase III. Laboratory data were to be collected for analysis by a central laboratory during two clinically important time windows. The first was day six to eight following chemotherapy, when patients returned for clinical assessments, including antiemetic efficacy.

At this time, early toxic effects of chemotherapy may be identified. A later assessment was obtained between days 19 and 29, when patients are typically evaluated prior to a second round of chemotherapy and when toxic effects, such as prolonged myelosuppression, can be identified.

These protocol-mandated assessments were supplemented as needed by additional measures that could be sent to local laboratories or to the central lab. The investigator was responsible for assessing all laboratory data and recording as clinical or laboratory adverse experiences any clinically significant findings.

Adverse changes in laboratory and clinical parameters may be ranked according to National Cancer Institute; that is, NCI, common toxicity criteria based on their severity. The criteria established four levels of increasing toxicity, grades 1 through 4.

All of our data collected through the central laboratory were evaluated according to NCI criteria. However, the local laboratory data were not

included in the NCI assessments.

This slide depicts the incidences of any elevation of any serum creatinine in the first line of the table followed by categorization of these elevations according to the four NCI severity grades indicated in the left-hand column. The incidences of patients with any elevation in serum creatinine were very similar between groups, both at the earlier and the later time points.

More than half of the early elevations had resolved my the later assessment. The NCI severity profile of changes was also very similar between the groups at both time points. And no findings ranked in the most severe category.

In summary, there were no apparent differences in the nephrotoxicity of cisplatin due to aprepitant as evidenced by the findings with serum creatinine. In addition, there were few neurological adverse experiences and no differences between groups in terms of neurotoxicity or ototoxicity.

As discussed earlier, potential changes in the toxicity of non-cisplatin chemotherapies were

assessed by evaluation of adverse reaction profiles typical of these agents. For example, this slide displays the occurrence of neutropenia in the aprepitant and control groups overall and according to NCI toxicity criteria during cycle 1 of chemotherapy.

As with creatinine and other laboratory parameters, blood counts for NCI assessments were obtained during the day 6 to 8 and 19 to 29 time frames. Again, laboratory adverse experiences could, nevertheless, be reported at any time in patients for whom additional local laboratory studies were performed.

There were no clinically important differences between the aprepitant and control groups with respect both to overall incidences of neutropenia shown in the first line of the table or to the incidences within each NCI severity grade. There was slightly more neutropenia in the control group at the day 19 to 29 assessment, but the incidences of grades 3 and 4 neutropenia were essentially the same.

Unlike the findings with creatinine, neutropenia was more common during this later

assessment period, reflecting the expected time course of changes in hematological parameters following bone marrow suppression by chemotherapy.

The data provided no evidence of differential chemotherapy-induced toxicity in the aprepitant group based on the similarities in neutrophil counts. A further assessment of the effects of aprepitant on the toxicity of concomitantly administered therapies based on occurrence of the pre-specified adverse experiences discussed earlier is shown on the next slide.

This first group of adverse experiences, which includes infections, dehydration, hematological toxicities, as well as fever and febrile neutropenia, reflects chemotherapy-induced adverse effects. There were no clinically important differences between the aprepitant and the control regimens.

The second group of adverse experiences, reflecting potential dexamethasone or corticosteroid-induced toxicity, also occurred with very similar frequencies in the two treatment groups.

In summary, assessment of pre-specified

adverse experiences supports a lack of significant interaction between aprepitant and concomitantly administered chemotherapies or glucocorticoids.

Earlier, Dr. Petty characterized aprepitant as a moderate inhibitor of CYP3A4 similar in potency to diltiazem, which should not affect the toxicity of concomitantly administered chemotherapy agents. We sought to confirm this by evaluating the safety profile of aprepitant separately in the subgroup of patients receiving chemotherapies that utilize the enzyme CYP3A4 as at least one pathway in their metabolism.

The relevant patients in our clinical trials received etoposide; the vinca alkaloid vinorelbine; taxanes, including paclitaxel and to a smaller extent the **taxel; and rarely irinotecan and ifosfamide. Data assessed include clinical and laboratory adverse experiences and hematological toxicities, in particular.

I will review our neutropenia data in the entire subgroup of patients and separately in patients receiving etoposide, vinorelbine, and paclitaxel, the

individual CYP3A4 metabolite chemotherapies most frequently administered during Phase III.

Approximately half of the patients in the Phase III trials received a concomitant therapy metabolized by CYP3A4, as shown by the N's in this table. During cycle 1, the overall incidences of adverse experiences were virtually identical, approximately 74 percent, in the aprepitant and control groups in this subgroup of patients who received, in addition to cisplatin, any concomitant chemotherapy metabolized by CYP3A4.

The overall frequencies of pre-specified adverse experiences indicative of chemotherapy are glucocorticoid-induced toxicity or serious adverse experiences, also showed little difference between groups. There were no changes characterized as serious laboratory adverse experiences in these patients.

My next slide displays the occurrence of neutropenia graded according to NCI toxicity criteria in patients who received chemotherapy metabolized by CYP3A4. The incidences of neutropenia during the

earlier and later evaluation periods were generally similar in the two treatment groups. There was a small excess of neutropenia in the control group at the day 19 to 29 assessment, primarily falling into the 2 milder NCI categories with no differences in the more severe grades.

Based on the incidence and severity of neutropenia at these two time points, there was no change due to aprepitant in the hematological toxicity of chemotherapy metabolized by CYP3A4.

This slide depicts the frequencies of neutropenia of grade 2 or greater; that is, less than 1,500 per millimeter^3, in all patients who received CYP3A4 metabolized concomitant chemotherapy, shown on the left, this being the percent of patients, and in those receiving the 3 most commonly administered individual chemotherapies metabolized by this pathway.

Etoposide was the most common. The N's are shown at the bottom for each of these chemotherapies. Substantial numbers of patients receive vinorelbine, the second most common CYP3A4-metabolized concomitant chemotherapy. And

paclitaxel was also administered frequently.

During the cycle 1, day 19 to 29 assessment, which is a measure of prolonged and clinically important myelosuppression, there were no noteworthy differences in the occurrence of significant neutropenia among any of these patient subgroups.

As noted, in addition to the NCI gradings of central laboratory data, investigators were also instructed to record clinically important laboratory findings as adverse experiences.

This slide depicts all adverse experiences of neutropenia for the patients described on the previous slides. As with the NCI characterizations, the incidences of neutropenia adverse experiences also showed no clinically important differences in the subgroups of patients receiving any CYP3A4-metabolized chemotherapy or in the individual subgroups representing the three most frequently administered agents.

In summary, during Phase III, we conducted an extensive evaluation of more than 250 patients per

group, who received additional chemotherapy metabolized by CYP3A4. We saw no pattern of clinically important changes between the aprepitant and control regimens in these patients based upon evaluation of overall and subcategories of clinical and laboratory adverse experiences and of neutropenia, in particular.

In addition to categorizing patients by whether they receive concomitant therapies, we also evaluated standard patient demographic subgroups according to age, gender, race, and primary cancer diagnosis. The data, which are presented in your background package, support the conclusion that the aprepitant regimen has a consistently favorable safety profile across these various demographic subgroups.

Thus far I have presented data describing our experience with aprepitant during an initial cycle of chemotherapy. Cancer patients typically receive initial followed by repeat cycles of chemotherapy. Therefore, the Phase III studies evaluated aprepitant over multiple courses of chemotherapy, up to a total of six cycles per patient.

During multiple-cycle extensions, patients continued on the same chemotherapy and antiemetic regimens with which they were treated during cycle 1. Safety data collection during multiple cycles included the most critical parameters according to investigators and consultants and by prior agreement with FDA; that is, clinical adverse experiences defined as drug-related or serious, and those causing the patient to discontinue further participation in the study. In addition, laboratory evaluations were obtained at the day 19 to 29 visit.

A large number of patients received treatment during multiple cycles. Over 400 patients in each group continued beyond cycle 1 and approximately 150 patients were treated for a total of 6 cycles of chemotherapy in the aprepitant and control arms, as noted in the safety update to the NDA.

The safety findings over multiple cycles confirm the favorable profile observed during cycle 1. This slide summarizes the incidences of drug-related or serious adverse experiences and those associated with patient discontinuations as well as serious

laboratory adverse experiences and deaths. None of the numerical differences between the groups was judged to be clinically significant. And there was no pattern of clinically important adverse events with the aprepitant compared to the control regimen.

The next slide illustrates the neutropenia observed during multiple cycles of chemotherapy. The graph illustrates the potential for aprepitant to affect the toxicities over time of concomitantly administered chemotherapies based on the occurrence of neutropenia over the course of six chemotherapy cycles.

The bars display the percentage of patients with neutropenia of NCI grade 2 or greater; that is, less than 1,500 per cubic millimeter at days 19 to 29. During each of the six cycles, the percentages of patients with neutropenia were remarkably similar, indicating that the hematological toxicity of concomitant chemotherapies does not change over multiple-cycle treatment with aprepitant. Overall, the adverse experience profiles and laboratory data confirm that the good tolerability

observed during cycle 1 with aprepitant extends over multiple cycles of chemotherapy.

In summary, the aprepitant regimen was well-tolerated with incidences of adverse experiences generally similar to standard therapy control. Aprepitant did not significantly alter the toxicity of concomitantly administered cisplatin or other chemotherapy agents, whether or not metabolized by CYP3A4. And there was no evidence of increased glucocorticoid toxicity.

There were no clinically important differences in the safety and tolerability profile of aprepitant based on age, gender, race, or primary cancer diagnosis. And aprepitant was well-tolerated during multiple cycles of chemotherapy.

SUMMARY AND CONCLUSIONS

DR. REINES: I would like to conclude this presentation to the advisory committee by sharing our perspective on the role of aprepitant in the supportive care of cancer patients receiving highly emetogenic chemotherapy.

When patients are diagnosed with cancer,

they are immediately confronted with the reality of having a life-threatening disease. Next, they must begin to consider the prospect of undergoing treatments that may be debilitating and disruptive to their lives at a time when they may not be physically impaired by the cancer itself. Clearly, at this time patients would like to preserve their ability to function normally. The symptoms of chemotherapy-induced nausea and vomiting may reduce their chances of doing that.

Since 1991, symptoms of highly emetogenic chemotherapy have been partially preventable by use of 5-HT_3 receptor antagonists. These drugs were quickly recognized as important therapeutic advances. However, despite their use, many patients still experience nausea and vomiting after emetogenic chemotherapy.

Patients still rank nausea and vomiting among the most distressing symptoms caused by chemotherapy. In particular, delayed symptoms often occur when patients are at home following each cycle of chemotherapy. And they remain difficult to treat.

These Kaplan-Meier curves, which Dr. Horgan presented earlier today, illustrate **patients in the control groups of our Phase III clinical trials. The curves show the percent of patients who remain free of emesis and the need for rescue medication.

By the end of day one, this proportion has already dropped below 70 percent. And after the five-day observation period following their chemotherapy, half or fewer patients in each control group were fully protected, indicating additional loss of control during the phase of delayed symptoms.

The graphs clearly illustrate the need for better antiemetic therapy since all of these control patients were treated with the best currently available treatment: a combination of a 5-HT_3 antagonist and a corticosteroid.

Aprepitant was developed to address this need. Over the course of seven years, we studied more than 3,000 patients, including more than 1,400 in cancer chemotherapy trials. We chose to develop aprepitant as an essential component of an antiemetic

therapy regimen to be used in conjunction with other antiemetic agents. In that way, we were able to achieve unprecedented efficacy during both the acute and delayed phases following highly emetogenic chemotherapy regimens.

The efficacy of aprepitant observed during cycle 1 was sustained over multiple-cycle treatment. In all trials, aprepitant was very well-tolerated.

Safety was demonstrated across a broad range of aprepitant doses in the presence of various chemotherapeutic agents, in addition to cisplatin, and with two different 5-HT_3 receptor antagonists. The overall safety and tolerability of a three-day aprepitant regimen was confirmed in the Phase III clinical trials.

Returning to the Kaplan-Meier curves, which now also illustrate in yellow the results for the aprepitant regimen, we can clearly see the marked clinical efficacy observed in the Phase III development program.

More than two-thirds of the patients who received the aprepitant regimen were protected from

emesis or the need for rescue therapy over the entire five days following their chemotherapy. This is a marked advance over the current standard of care, again shown in blue.

The effect of aprepitant begins within 24 hours during the acute phase of chemotherapy and is especially pronounced in prevention of delayed symptoms over the next four days.

In conclusion, the aprepitant represents the first of a new class of therapy, a Substance P antagonist at central NK_1 receptors that features a novel mechanism of action with distinct clinical benefits. As a cornerstone of a regimen for prevention of nausea and vomiting due to highly emetogenic chemotherapy, aprepitant provides marked symptom reduction and improves upon the best available antiemetic therapy.

We hope that this new medicine may alter an enduring perception of cancer chemotherapy by allowing most patients to undergo emetogenic treatment without the inevitable fear of nausea and vomiting.

We are pleased to have had the opportunity

to share our data with you this morning. In closing, I would like to leave you with our proposed indication for aprepitant. Thank you.

CHAIRPERSON CAMILLERI: Thank you very much.

QUESTIONS AND PRESENTATIONS

CHAIRPERSON CAMILLERI: I would like to propose that we spend about ten minutes now addressing some questions. I would like to thank the company representatives for their very comprehensive and clear presentations to us.

And I would like to propose to the committee members that in the first part of the questions to the company we focus on issues that are not already entertained in the brief that Dr. Justice provided us. For example, I am sure we are going to come back later in the presentations from the agency as well as perhaps questions this afternoon as we discuss these several issues. We are going to need to address the specific questions that you proposed pertaining to efficacy in nausea and also the proportion of patients with other inducers of

cytochrome p450 3A4, which may not have been over-represented in the patient groups here.

So I would like the committee members in this first part of the questioning to focus on specific issues pertaining to the presentations we have just heard and not the general issues that were entertained in Dr. Justice's opening arguments.

So the other thing I would like to do in the next 10 to 15 minutes before we adjourn for a break is to try to focus the questions first on areas pertaining to clinical pharmacology. Then we will have the break. Then we will come back and deal with clinical efficacy and safety issues.

So if that is acceptable to **everyone -- and I am assuming it is -- I would like to ask my colleagues on the committee whether you have any questions pertaining to pharmacology. Perhaps we will address the questions on 3A4 and numbers, et cetera, later, when we discuss this with the agency's presentation.

Dr. LaMont?

DR. LaMONT: Yes, sir. I have a question

about figures 28 and 39. There seems to be no data provided on figure 28 for aprepitant plasma between hour 24 and 48. Also, on slide 39, there is no data for days 2, 3, and 4, although you're giving the drug on those days. I just wonder why those data weren't included or if they're soon to be unrevealing or --

DR. PETTY: Actually, if I can answer the question, if we could first go to slide number 28, please? In this particular study, the data actually weren't collected. We did not collect the detailed profile between 24 and 48 hours. So the plasma samples that were collected were from zero to 24 hours the first day of the regimen and from 48 to 72 hours the last day of the regime. So there is not a detailed plasma profile in between day one and day three.

DR. LaMONT: Would you predict it would go up?

DR. PETTY: No. We would --

DR. LaMONT: Would it exceed the *p* count day one?

DR. PETTY: We think that would be

unlikely based on the effect that we see on day three. We also observe with the longer dosing of the five-day regimen that the trough concentrations remain relatively constant.

And if we could go to slide 39, I believe it was?

DR. LaMONT: Thirty-nine.

DR. PETTY: Yes. And this experiment was conducted in a similar fashion. The profiles for dexamethasone were collected only on day one and day five, the first day and the last day of the regimen.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Metz?

DR. METZ: Yes. Thank you.

I noticed in that slide that was just shown right there that you reduced your dose of the steroid for the therapeutic arm of your trial because of the induction that occurs. Do you have any data without steroids at all?

I am interested in whether the effect on your delayed response is steroid-mediated because that is the proposed action of the steroids or whether you

are just boosting the effect of the steroids, you are lowering the dose but you are getting your added effect that way. So do you have any data at all without the steroids?

I realize your program is designed to add to an existing regimen, but it seems to me conceivable that you could have a regimen without a steroid, which in itself has potential side effects.

DR. PETTY: Well, for the effect that we see here with dexamethasone, the approximate twofold increase, we adjusted downward for the dose of dexamethasone to provide balanced dexamethasone exposure in the Phase III studies. And the Phase III studies were conducted with dexamethasone in both arms.

CHAIRPERSON CAMILLERI: So, to clarify that point, I think what Dr. Horgan is going to say is that the aprepitant-treated dose with steroid dose with the aprepitant group was lower than in the control group. Is that correct?

DR. PETTY: Correct. They're the same level.

DR. HORGAN: Right. And just to clarify the background to your question and how we approached it philosophically in the program, we did a monotherapy study first, which clearly showed the efficacy of aprepitant in the prevention of delayed symptoms without any confounding factors.

Then, when we did a variety of Phase II studies, we studied aprepitant in the context of concomitant corticosteroid therapy on day one. And we again consistently showed efficacy in the prevent of delayed symptoms.

Then when we moved into the latter part of the program, when it was clearly the established standard of care and recommended, for example, in consensus guidelines that corticosteroids be administered during the delayed phase, we evaluated aprepitant in the context of addition to a standard therapy regimen.

Now, it's correct. We did not define precisely the relative contributions in the later part of our program provided by aprepitant and dexamethasone in the prevention of delayed. However,

we clearly demonstrated prior to that that aprepitant has a substantial effect in the prevention of delayed symptoms.

DR. METZ: Except that you don't have any data without steroids except for your monotherapy trial.

DR. HORGAN: Right.

CHAIRPERSON CAMILLERI: Dr. Desta?

DR. DESTA: Yes. I have a question of whether you have screened for CYP2C8 and 2B6 because CYP2C8, even though paclitaxel is metabolized by 3A, there is also a component of 2C8. So at least the *in vitro* data must be done for this purpose, I guess.

And the other one is CYP2B6. We know that cyclophosphamide and partly absorbed ifosfamide, these drugs are primarily, including thiotepa also, metabolized by 2B6. I wonder whether we have some at least *in vitro* screening data for these isoforms.

The second question I have is, you mentioned address does not affect the PK of your drug. And I saw in one of the documents that there is a several-fold increase in AUC of aprepitant.

So when do you say it is not clinically important in age, the group with, if I am correct, a 74 percent increase in AUC? Is that correct?

DR. PETTY: You are referring to the effect of other drugs on aprepitant?

DR. DESTA: No, no.

DR. PETTY: I'm sorry. I didn't --

DR. DESTA: On age.

DR. PETTY: Age? Oh, sorry. Yes.

DR. DESTA: Yes. And my last question is, you talk about the exposure better, and you have shown PET data in your data analysis. I wonder whether you did some time course of that because that will guide you probably to the dosing interval of the drug. After a single dose, did you do some sort of time course for the PET analysis?

DR. PETTY: If I can answer your first question first?

DR. DESTA: Okay.

DR. PETTY: You asked about effects, potential effects, of aprepitant on CYP2B6 and CYP2C8.

DR. DESTA: Yes.

DR. PETTY: We have not specifically evaluated those in our *in vitro* screens of microsomal turnover, although we have evaluated, in addition to CYP3A4, several other cytochrome p450 enzymes. And there was no evidence of inhibition of aprepitant of those cytochrome p450 enzymes. It exclusively had an effect on CYP3A4.

So specifically, no, we have not evaluated CYP2B6 and 2C8 *in vitro*, although our clinical data would suggest that there doesn't appear to be a significant effect of aprepitant on drugs metabolized by those enzymes.

For your second question regarding age, we specifically looked at the potential effects of age on the pharmacokinetics of aprepitant in a study in elderly subjects as well as a comprehensive analysis of all of our Phase I data.

We found very slight effects, at most perhaps a 30 percent increase in the AUC of aprepitant. We have found that in our clinical program, aprepitant is a rather wide therapeutic index drug. And, as Dr. Reines pointed out in some of our

other studies with higher doses of aprepitant given for much longer periods of time, we found that plasma concentrations seven-fold higher than those achieved with this regimen have been very well-tolerated. So we would conclude that a 30 percent increase in AUC would not be clinically important.

And, to answer your third question, with regard to the PET studies, no, we have no specifically done single-dose PET studies. Given the complexity of those studies, we were essentially only able to measure the drug concentration and brain occupancy effects at a single time point 24 hours after the last dose of aprepitant. Based on a dose-response, the plasma concentrations clearly correlated very well with the brain occupancy.

CHAIRPERSON CAMILLERI: Dr. Cryer?

DR. CRYER: Thank you.

This is also for Dr. Petty. So one of the questions which we will be focusing on is the potential for interaction of aprepitant with chemotherapy, which is obviously similarly metabolized by CYP3A4. So in that light, I would like to go back

to slide 44, if we could.

The question is, as I understand it, these data are data with aprepitant with its effects on docetaxel plasma concentrations. And this **issue is in your application and clinical practice, it is proposed to use aprepitant as combination therapy with the 5-HT_3 antagonists as well as with the corticosteroids. And so I really can't take this data and generalize it to what we might expect to see in clinical practice.

So do you have any data with the combined therapy of the three, the corticosteroids, the 5-HT_3 antagonists, along with aprepitant, with regard to its effects on chemotherapeutic agents that would be metabolized by CYP3A4?

DR. PETTY: Most of our drug interaction studies have been done with aprepitant by itself to provide as clear a result as possible. We know that the agents that are co-administered in the regimen, the 5-HT_3 antagonists and the steroids, do not inhibit CYP3A4 activity, for example. There is no evidence of that.

So we would not anticipate a different type of interaction when the three agents are used together, but typically the results that we see with aprepitant used by itself are fairly consistent with that, at most a moderate effect on CYP3A4.

CHAIRPERSON CAMILLERI: Dr. Fogel?

DR. FOGEL: Thank you.

I have a question about the central binding of aprepitant. The physiology related to vomiting indicates involvement of the vagal complex in the area postrema. The PET studies that you showed on slides 29 through 31 show the cortex. And PET scans aren't particularly effective in showing the vagal complex.

Do you have any data regarding blinding studies looking at the effects of aprepitant on NK_1 receptors in the dorsal vagal complex and the area postrema?

DR. PETTY: This particular section, as you point out, is through the striatum and one area of the cortex. We have examined other areas of the brain. The PET scans can be examined throughout the

entire area of the brain.

And we find that aprepitant does displace the binding of the tracer and from the receptor throughout all regions of the brain. And we have demonstrated that this tracer does bind in the brain stem to the areas in question.

CHAIRPERSON CAMILLERI: A subsidiary question, I think the brief shows that there are autoradiographic studies that are more focused on dorsal motor nucleus of the vagus and nucleus of tractus solitarius.

So can you tell us whether the other nuclei are like ambiguous in dorsal motor nucleus, rather than the NTS, also have displacence of NK_1? Because those would be perhaps more relevant in the context of the retching and the vomiting.

And a question for you, Dr. Petty. I saw the occipital cortex of the cerebellum also lights up. So are there any toxicity studies looking at cerebella or occipital visual cortical functions when you give the NK_1 antagonist?

DR. HARGREAVES: Sir, I'm Rich Hargreaves

from pharmacology at Merck.

The answer to your question is the PET resolution when we analyzed the data was for the brain stem only. The resolution is too poor to distinguish between those nuclei. And so we have a parallel displacement looking over the general area of the dorsal motor nucleus, but we can't distinguish specific neuronal groups.

CHAIRPERSON CAMILLERI: But, to help the questioner, you do have data in your profile, I believe, because I read it in the brief, that there are autoradiographic studies in other animals that show binding to dorsal motor nucleus of vagas or dorsal vagal complex which would be relevant in its antiemetic effects.

DR. HARGREAVES: Absolutely. I mean, the NK_1 receptor is present throughout those nuclei. And there is a parallel displacement in certainly the preclinical species, such as the ferret.

CHAIRPERSON CAMILLERI: Thank you.

Question about the occipital cortex or whatever is lighting up in the back of the brain?

DR. PETTY: Yes. As shown on the PET scans, the tracer binds to NK_1 receptors within their known distribution, which would include many cortical areas. Actually, they are a very low concentration of receptors in the cerebellum. And the tracer actually reflects that as well, although it is not displayed on that particular slide.

We have not observed, particularly in our clinical studies, again, at doses much higher and given for much longer duration of time, any adverse experiences that would be related to potential effects on vision.

CHAIRPERSON CAMILLERI: Ms. Cohen? Thank you.

MS. COHEN: As you know, I'm the consumer member. So you have to bear with me while I ask you some questions.

First of all, I noticed that in your clinical trials, you did four children. What percentage of the members in your trial were special populations? I guess I am part of the special population.

And I have a few more questions. Would you like me to give them all at once? Do you mind?

CHAIRPERSON CAMILLERI: If they are not on clinical pharmacology, can I suggest that we pick them up later?

MS. COHEN: Well, I do have a curious question. On chemotherapy, on the drugs that are used in chemotherapy, how many drugs did you test your aprepitant against?

Also, is there a common denominator within all of the chemotherapy drugs that do induce the nausea and the vomiting?

CHAIRPERSON CAMILLERI: Thank you.

DR. HORGAN: I will answer your second question first. We used cisplatin because it is the prototypic drug for evaluating a novel antiemetic. The precise mechanism of how cisplatin and other chemotherapeutic agents invoke nausea and vomiting is not completely understood.

As Dr. Petty mentioned, cisplatin and some of the other therapeutic agents have been shown to invoke the release of serotonin from the

enterochromaffin cells in the gut. And clearly they are likely to elicit the release of Substance P acting at the NK_1 receptor in the brain stem.

Apart from those two mechanisms, it is not really understood what the precise mechanisms are that are responsible for evoking the symptoms.

Does that answer your question?

MS. COHEN: If I'm allowed to say something more? To a certain extent. And that in itself is a puzzle to me in terms of how this all works, obviously.

I am also interested in how you dealt with the patients who were getting chemotherapy in the normal controls and how you can simulate the kinds of things that would happen.

DR. HORGAN: Well, the assessment of efficacy was done in patients receiving cancer chemotherapy. So all of our assessments of efficacy were done in that patient population. So we were doing clinical trials in the context of clinical practice.

MS. COHEN: And the special population,

what percentage of that?

DR. HORGAN: In fact, we actually enrolled in the Phase III program a total of six adolescents. The data are mentioned in the background for four. Those were I think the only patients that you would describe as being special that didn't conform to the general enrollment criteria of the general trials.

MS. HOGAN: Well, in the aging population, like me, how many of those did you have?

DR. HORGAN: Well, that was included in our general population.

MS. HOGAN: Yes, but --

DR. HORGAN: And that was --

MS. HOGAN: Thank you.

DR. HORGAN: -- more than 30 percent of the patients.

MS. HOGAN: At what age? Do you have any idea?

DR. HORGAN: It would be 65. Approximately 30 percent were more than 65.

MS. HOGAN: Thank you very much.

CHAIRPERSON CAMILLERI: Dr. McLeod?

DR. McLEOD: A clinical pharmacology question for Dr. Petty. It's two different questions, each with eight parts.

(Laughter.)

DR. McLEOD: No. There are two specific questions that are interrelated. And they really go around the area of variability.

First of all, if you could maybe walk us through your selection of a fixed dose versus milligrams per meter^2 or other individualized dosing approaches and also talk a little bit about the linearity of the pharmacokinetics of this agent across the different doses that were utilized, recognizing that the starting dose for patients may change as there is further experience gained with this agent.

DR. PETTY: If I can address your second question first? I believe your first question is related to the dose of chemotherapies, if I'm not mistaken. Sorry.

DR. McLEOD: No. All about the dose of this agent.

DR. PETTY: Of aprepitant?

DR. McLEOD: Yes.

DR. PETTY: I see. In that case, the doses of aprepitant used at 125-milligram, 80-milligram are the only doses that we are proposing for this particular indication. They are not adjusted per meter^2.

We have demonstrated that for these two doses, there is slight nonlinearity in the pharmacokinetics of the drug in that there are slightly higher plasma concentrations as the dose is increased.

We did study other doses as well. And we determined with this particular regimen with the dose of 120 milligrams on day one and 80 milligrams on subsequent days that it provides a relatively consistent plasma concentration across the time interval that we're looking.

We did study the kinetics in elderly patients with renal insufficiency, hepatic insufficiency, found relatively minor effects that would not necessitate dose adjustment of aprepitant. So we would not recommend dose adjustment for other

situations.

DR. McLEOD: When you look across the more extensive doses that you used during your Phase II and Phase I programs, when you talk about nonlinearity, how dramatic is this nonlinearity as you expand the dosing?

DR. PETTY: Well, for these two doses specifically, which are the only two doses we're proposing for clinical use, if I can refer to one of my slides here -- I'm sorry. It will take just a minute. We're getting there. Just a second. If we could have slide 1324, please?

CHAIRPERSON CAMILLERI: I'm wondering whether this might be a good time to have a very brief break, let you find the information you want, and then come back to the same questions from Dr. McLeod. And then Dr. Cryer will resume questions as well.

Let's take a five to ten-minute break. And we will be back at 10:50.

(Whereupon, the foregoing matter went off the record at 10:41 a.m. and went back on the record at 10:53 a.m.)

CHAIRPERSON CAMILLERI: I would like to bring the meeting back to order.

Thank you, Dr. Petty. You are back at the podium.

Dr. McLeod, would you like to remind us of the two questions? And then Dr. Petty will respond.

DR. McLEOD: The questions really are posed around trying to understand the degree of variability in pharmacokinetics across the doses that have been evaluated, including the doses which you have put forward for the indication. So understanding the linearity across those doses and then within that will help answer the question of a fixed dosing versus dosing individualized to something like body weight or body surface area.

DR. PETTY: Sure. If I can have slide 1332, please? This was a study actually designed to assess the dose proportionality of aprepitant. In this case, it was given as a colloidal dispersion.

What was done was in healthy subjects, doses as low as 10 milligrams up to as high as 600 milligrams, which spans the dose range that we are

proposing -- as you can see, this was the AUC in those subjects.

And it was fairly linear throughout the entire range here. So, at least with respect to the area under the curve and the drug, it is fairly linear over this particular dose range.

DR. McLEOD: So the nonlinearity referred to earlier, was that looking at intra-patient differences in pharmacokinetics when they got the loading dose versus the subsequent doses or is it just a population mean at the --

DR. PETTY: No. That was only comparing two doses in a healthy population, a pharmacokinetic study.

CHAIRPERSON CAMILLERI: Dr. Cryer?

DR. CRYER: I just wanted to briefly come back to this issue of pharmacokinetics with the combined antiemetic regimen. So from your clinical trial experience of patients who received the combined antiemetic regimen, there are no pharmacokinetic evaluations of the chemotherapy regimen. Was that correct?

DR. PETTY: Correct. In cancer patients, in the Phase III studies, pharmacokinetic data were not collected, although the safety profile of patients who were receiving the standard regimen both on ondansetron and dexamethasone compared to the aprepitant regimen, in which all three agents were given indicates that the safety profile was similar between the two groups. And we would conclude that there probably were not significant pharmacokinetic interactions on that basis.

CHAIRPERSON CAMILLERI: Dr. Kelsen?

DR. KELSEN: Can we ask a nonclinical pharmacology question yet?

CHAIRPERSON CAMILLERI: Are we done with clinical pharmacology? Dr. Houn?

DR. HOUN: Hi. Florence Houn.

I am just interested in Dr. Malcolm Rowland's opinion on slide 44 and his interpretation of what he thinks is happening.

DR. PETTY: Can we have slide 44, please?

DR. ROWLAND: Yes. This is obviously a study and it was indicated an ongoing study of looking

at whether or not the target aprepitant affected docetaxel. These are obviously gained as you go along in the clinical study. They're not easy to do, and you couldn't do these in normal volunteers.

What this basically is saying is that there is virtually no effect of the aprepitant on the docetaxel kinetics in this regimen. This is a clinical dosage of the drug.

So the right-hand side is basically to look at the issue which does come up, and that is variability. You can get people high or low. And what you are seeing is that looking at any one with respect to themselves as individuals, there are no real changes that you can observe.

DR. HOUN: Is this expected?

DR. ROWLAND: Yes. The issue was a lot of the chemotherapeutic agents are given intravenously. And I think the data, the body of data, coming out is that aprepitant doesn't have a strong effect on inhibition systemically. Its main effect appears to be at the inner wall level. I think that is what we are seeing with the data in general.

CHAIRPERSON CAMILLERI: Dr. Levine?

DR. LEVINE: Just had a question about the rescue medications, whether it was a variety of benzothiazides, whether it was up to the discretion of the individual investigators, or if they all were limited to one, compazine or something else.

DR. HORGAN: The choice of a rescue medication was entirely left to the discretion of the investigator. We did provide a list of recommended medications, but the specific agent chosen was based entirely at the discretion of the investigator.

And a wide variety were used. More than 40 percent of the patients who received rescue received metoclopramide, and then the other specific agents were all used in less than 10 percent of patients. There was a wide variety.

What we were really meticulous about was the instructions about when patients could take rescue. And that's where we really focused the precision of our instructions.

CHAIRPERSON CAMILLERI: I think we should ask Dr. Horgan to stay there now because we are going

to open the questions for clinical efficacy. Dr. Kelsen, you had the first question.

DR. KELSEN: So this touches a little bit on the point of oral and intravenous drugs. You have indicated that this agent has effects on some drugs and not on others in the clinical pharmacology. And we talked a lot about toxicity. And it looks like it doesn't affect chemotherapy toxicity that much.

Do you have data on chemotherapy effectiveness? About 40 percent of your patients had lung cancer. I assume a number of those regimens were the lung cancer regimens. Do you have data on outcome to indicate that it doesn't affect therapeutic efficacy of the treatment of the disease?

DR. HORGAN: We did not formally assess the efficacy of chemotherapy in these clinical trials. We followed the paradigm of the 5-HT_3 receptor antagonists.

As you mentioned, many of the patients had lung cancer, but they also had a wide spectrum of cancers. It's not possible in the context of a trial like this to formally assess the efficacy of

chemotherapy.

In general, the toxicities that we saw that would be predictably associated with chemotherapy were well-balanced between the treatment groups, indicating that there was unlikely to be any pharmacokinetic explanation as to why the efficacy of chemotherapy should be altered.

DR. KELSEN: There are about 200 patients in each group who had lung cancer, right? We don't have data on response rate or survival or anything?

DR. HORGAN: No. It wasn't possible given the heterogeneity of the patient populations, their specific diagnoses, their specific regimens. That has been the practice in these trials. It's not, as you know, to actually formally evaluate the efficacy.

DR. KELSEN: I guess my interest was the concern that there is an interaction with some pharmacokinetic interactions, but you have answered my question. Thank you.

MS. HOFFMAN: In terms of the pediatric population and clinical efficacy, one thing that I would like to say, I guess, is that you mentioned that

you didn't do a study arm without the use of steroids.

From the pediatric population, the impact of steroids can sometimes be as difficult to deal with as the nausea and vomiting from a parent perspective, the mood swings, the moon face, that sort of thing. So a study arm spanning the pediatric population without the use of steroids might be something to look at and to see the effectiveness of your study drug without steroids.

CHAIRPERSON CAMILLERI: Thank you for the comments.

Dr. Proschan?

DR. PROSCHAN: Yes. I was wondering. You measured nausea on a visual analog scale, but you presented results in terms of nausea less than five yes or no. I am wondering whether you did any kind of analysis of it in a continuous way.

DR. HORGAN: Yes. We have looked at nausea very comprehensively. And the bottom line is that, whatever way we look at it, we consistently see an advantage for the aprepitant regimen.

And, actually, if I could have slide 203?

The reason we used the visual analog scale was because of its greater sensitivity. And if I can just walk you through this slide, which shows the data for both protocols combined? And it shows the distribution of maximum visual analog scale ratings over each of the five days, the maximum reading over each of the five days in which patients gave recordings.

So on the horizontal axis, you see the peak nausea score. And then on the vertical axis, you see the percentage of patients. So, for example, if you look at a peak nausea rating of 40 and you look at the vertical there, what you are seeing is this represents the percentage of patients who have a peak nausea score of 40 or less. And you can see that there are more patients in the aprepitant group who have a peak score of 40 or less.

Now, where we drew our lines for our two pre-specified endpoints were at 5 and at 25. You see at those cutoffs, we had an advantage in the aprepitant group.

Now, we could have drawn those vertical

lines right across the spectrum of peak nausea scores. And we would ultimately have gotten the same outcome.

We pre-specified those for the reasons that I gave because there were prior precedents. And they correlated with impact on daily life. And this difference for the analysis of the continuous data was statistically significant.

CHAIRPERSON CAMILLERI: Dr. Metz?

DR. METZ: Thank you.

I was thinking about what Dr. Kelsen was saying. I don't know if it has been fully addressed. Excuse the naivete of all of this, but I don't know anything about NK_1 receptors. Does anyone know where in the body NK_1 receptors are distributed? Especially are there any NK_1 receptors on any kind of tumor types at all? Has anyone looked?

DR. HORGAN: There is some data that NK_1 receptors are expressed by tumor cell lines, gliomas, some breast cancer lines, and some small cell line cancer lines.

The significance of those is not definitively known. There is some suggestion that

blockade of those receptors may alter the growth characteristics, reduce the growth of those tumor cell lines. And that is basically the extent of the current knowledge with regard to that.

CHAIRPERSON CAMILLERI: Dr. LaMont?

DR. LaMONT: Yes. I have a question relating to emesis and nausea on slides 107 and 108. I am just trying to reconcile the data given in slide 107, which says that at week 6, approximately 75 or 80 percent of the aprepitant patients had no nausea; whereas, if we look in the left panel of slide 108, it looks like the percentage of patients with emesis is less than that.

I just don't understand. I am trying to reconcile these two slides and to understand the apparent decline in efficacy. So it's a two-part question.

DR. HORGAN: Okay. Well, the background to this is this is the assessment of efficacy during multiple cycles of chemotherapy. And there is a variety of ways to look at this data to provide insight into the efficacy profile.

The first one that we showed in 107 is the observed proportion of patients without emesis and without significant nausea. The information derived from the two questions that patients were asked at each chemotherapy cycle.

What we are illustrating here is a snapshot at each cycle of what the outcome was for those two variables. And it's not linked, the outcome in each cycle is not linked, to what happened in the preceding cycle. It's a snapshot at each cycle. This is the efficacy profile that we see.

I don't think that you can really make an inference so much as to what is happening, the trend over the cycles, within each treatment group. I think the key message here is the relative difference between the treatment groups at each individual cycle.

Then in the next slide, 108, this is a Kaplan-Meier approach. In this case, for the time to first emesis, a patient having emesis in the first cycle is obviously lost, then, in the analysis for subsequent cycles. So it's a different way of looking at the data. And the outcome at each cycle reflects

what is the outcome in previous cycles.

Again, the key message here is not so much the trend within each treatment group. It is the relative efficacy, the advantage afforded by aprepitant during each cycle. It is simply a different way of looking at the data.

CHAIRPERSON CAMILLERI: Dr. Brawley?

DR. BRAWLEY: Do you have any data about dose reduction chemotherapy cycle to cycle?

DR. HORGAN: Could you clarify?

DR. BRAWLEY: I am wondering if patients were given less chemotherapy in cycle 2 and cycle 3 versus cycle 1 or perhaps because of less nausea, maybe even the patients were able to get full doses of cisplatin in cycle 2 through --

DR. HORGAN: Right. We didn't actually look at the dose that was administered in subsequent cycles of chemotherapy. We didn't specifically address that question.

CHAIRPERSON CAMILLERI: Dr. Proschan, I will follow you.

DR. PROSCHAN: Okay. Thank you.

You know, in some of your slides, like the last one you show, you have got both of those protocols, 052 and 054, combined. And in others, you look at them separately. I don't mean to be cynical, but I am guessing that the combined ones are when you didn't have significance of either one separately.

DR. HORGAN: Well, the displays are really done for combined for reasons of convenience. We did not do statistical testing on the data for the multiple cycle. So these are displays of efficacy.

And the bottom line is that a similar picture was seen in the individual displays.

CHAIRPERSON CAMILLERI: Dr. Horgan, I have a question pertaining to whether the 40/25 regimen is really less effective. I would like to refer you to your charts 82 and 83 because there is something there that I don't completely understand.

DR. HORGAN: Here you see the 40/25 regimen has an overall complete response rate of 59 percent. In 83, next slide, please. Somehow when you look at the information separately for acute and delayed, it goes up from 59 to 76 and 64. And here

there doesn't seem to be a significant difference.

So my question to you is, is it true that the minimum effective dose perhaps or the maximum dose here is the 125/80 relative to the 40/25?

DR. HORGAN: Right. Well, the first part of your question, the apparent discrepancy, there isn't a precise correlation between efficacy in the acute phase and the delayed phase. There is a correlation, but it's not precise.

So some patients here who had controls during the acute phase of the 76 percent of patients would have gone on to have symptoms in the delayed phase and vice versa, which is why when you merge the two phases below, that the overall response that you're seeing, the 59 percent you mentioned, is actually lower than what you see in the delayed phase alone because the correlation is not precise.

And if you go back to slide 82? So what we saw in the data that we gathered in this study for the spectrum of endpoints that we used, there was consistently always a numerical advantage for the 125/80 milligram regimen versus the control regimen.

And then when we did a formal analysis for the primary endpoint of overall complete response, we saw a statistically significant difference here, justifying our selection of the 125/80 dose.

CHAIRPERSON CAMILLERI: Ms. Cohen?

MS. COHEN: I want to make sure I understood Dr. Kelsen's question and your answer to him in terms of the effectiveness against medication or an anti-chemotherapy. You didn't study if there was any relationship to the efficacy of the drug itself affected by aprepitant?

DR. HORGAN: We did not formally assess whether aprepitant altered the efficacy of chemotherapy.

MS. COHEN: Well, then would it not be appropriate to tell a patient that "We can reduce your nausea and vomiting, but we don't know the effect of the chemotherapy, how it affects the chemotherapy"? I would want to know that. I think I am entitled to know that. Wouldn't you think so as a patient?

DR. HORGAN: Well, the data we have on the drug strongly suggest that there is no interference

with the pharmacokinetics of the chemotherapy that the patient is administered; in other words, the levels of the chemotherapy.

MS. COHEN: Well, was that specifically studied?

DR. HORGAN: Yes.

MS. COHEN: Go ahead. And I have one other question, then. I didn't know if there were other chemotherapy drugs that you didn't test with aprepitant. That would be my second question.

DR. REINES: Sorry. If I could comment on your question because it is so critical? If we could have slide 133? Although it is not possible in studies of this size and duration to formally assess the efficacy of the chemotherapy regimen on the cancer, as a surrogate of that, we look carefully at the toxicity due to the chemotherapy because the efficacy would be expected to be related to how much toxicity the chemotherapy is causing. This essentially is a measure of the exposure the patient gets to the chemotherapy at the level of the bone marrow.

As you can see, I emphasized in my presentation that there wasn't more neutropenia in the aprepitant group, but there is not less neutropenia either, which means that there should not be any less exposure in those patients.

And so, as a surrogate of efficacy since we couldn't measure pure efficacy of the chemotherapy regimen, we looked very carefully at parameters like this. And we didn't find any evidence that there might be a reduction in the exposure to the chemotherapy agent.

CHAIRPERSON CAMILLERI: Dr. LaMont and then Dr. McLeod.

DR. LaMONT: Yes. You list a death rate of 6.8 percent in the aprepitant group out of 413 patients versus 5.3 in the controls. I wonder if any of those deaths are attributable, in part or in total, to aprepitant.

DR. REINES: During the first cycle of chemotherapy, the death rate was 20 in the aprepitant group and 21 in the control regimen. So it was very evenly balanced. Over multiple cycles, we observed

the death rates that you described.

If we could go to slide 515, please? Sorry. If we go to 516 first, this shows the death rate by cycle beyond cycle 1. And, as you can see, there is no pattern there of an increase, although it does lead up to this small differential that you mentioned.

If we go to 517, this displays over the multiple-cycle data the percentages 6.8 and 5.3 and the primary causes. None of these were attributed to aprepitant. And they were virtually all attributed to the underlying disease in the patients.

CHAIRPERSON CAMILLERI: Dr. McLeod?

DR. McLEOD: My question is actually more probably for Dr. Horgan. There are three main components to chemotherapy-induced nausea and vomiting. The acute and the delayed phase you have presented the information on. I wondered if you had any data on the degree of anticipatory nausea and vomiting that occurred during cycles 2 and beyond as a way of understanding the level of control that the two arms evaluated had during the first cycle of

chemotherapy.

DR. HORGAN: Right. Unfortunately, we didn't formally assess that because, as I mentioned, our approach to the collection of efficacy data during multiple cycles was streamlined and simply reflected the two questions that patients were asked at the day six to eight clinical visit. So we didn't formally assess the incidence of anticipatory symptoms.

CHAIRPERSON CAMILLERI: Thank you.

I believe we have had enough questions on the presentation from the sponsors. I would like to invite the FDA presentation. The first presentation is on the clinical summary by Dr. Gary Della'Zanna. He will be followed by pharmacology by Dr. Jarugula.

FDA PRESENTATION

CLINICAL SUMMARY

DR. DELLA'ZANNA: Good morning. My name is Gary Della'Zanna. I'm a medical officer in the Division of Gastrointestinal and Coagulation Drug Products at the Food and Drug Administration.

I would like to take the time to introduce the other divisions involved in this presentation.

Dr. Wen-Jen Chen is a mathematical statistician from the Division of Biometrics II. And Dr. Venkat Jarugula is a clinical pharmacology reviewer from the Office of Clinical Pharmacology and Biopharmaceutics.

During today's presentation, I will give a brief background of aprepitant, touching on a treatment regimen and the proposed indication. Efficacy results will be presented for the **primary endpoint and some of the secondary endpoints that are relative to the proposed indication.

I will present the questions the agency has in regard to the dose of highly emetogenic cisplatin and our safety concerns for potential drug-drug interactions. Following my presentation, Dr. Jarugula will explain the metabolism of aprepitant in detail and the potential for drug-drug interactions.

On September 27, 2002, Merck and Company submitted a new drug application for aprepitant. Aprepitant is a New molecular entity that, if approved, would be the first in a new therapeutic class, the NK_1 receptor antagonist. At the time of

the submission, the applicant requested and was granted priority review status.

The proposed treatment regimen is a three-drug therapy that includes aprepitant in combination with a 5-HT_3 antagonist and a corticosteroid. The applicant has requested an indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic chemotherapy. Aprepitant would be the first drug to be granted an indication that includes the delayed phase of chemotherapy-induced nausea and vomiting.

One of the questions the agency has is in regard to the primary endpoint and whether the submitted data supports the proposed indication. The primary endpoint for both Phase III studies was defined as complete response in the overall phase. A patient was considered to have complete response if they did not vomit and did not require rescue therapy. The overall phase was from zero hours to 120 hours after the administration of cisplatin.

The complete response endpoint was

evaluated and analyzed for three distinct time periods, the overall phase being the primary endpoint with the acute and delayed phases being secondary endpoints.

Since the proposed indication is for nausea and vomiting in the acute and delayed phases, each were analyzed independently as secondary endpoints.

The agency reviewed the applicant's data and concurs with the results of the major analysis. The sponsor successfully demonstrated the aprepitant regimen was superior to standard therapy for the primary endpoint, complete response in the overall phase, as well as the secondary endpoints of complete response in the acute and delayed phases and the no vomiting endpoints in the overall, acute, and delayed phases.

Next slide. Results of the no nausea endpoints, however, were not as persuasive. This table displays the results of the no nausea endpoints for the two Phase III studies.

The nausea endpoints were evaluated for

three time periods using two separate criteria that were based on a 100-millimeter visual analog scale. The no nausea endpoint was defined as a VAS rating of less than five millimeters with no significant nausea being less than 25 millimeters.

I would like to draw your attention to the top portion of this chart for the no nausea endpoint. The no nausea endpoints were only statistically significant in the overall and delayed phases of study 054. The aprepitant regimen did not reach statistical significance in the acute phase of study 054 or any of the three phases in study 052.

Additionally, the no significant nausea endpoint, shown here on the lower half of this table, was only statistically significant in the acute phase of study 054 with an unadjusted *p* value of 0.01. Because several predefined secondary and exploratory endpoints were analyzed, the nominally significant results cannot be taken at face value due to multiple comparisons.

The agency agrees with the firm that the results of the nausea endpoints may have been affected

by the use of rescue therapy. Twenty-eight percent of the patients in the standard therapy group required rescue therapy compared to 18 percent in the aprepitant group.

Furthermore, time to analysis showed that the time interval for the use of rescue therapy was longer in patients in the aprepitant group than the standard therapy group.

However, since this would be the first time that the agency granted an indication for chemotherapy-induced nausea and vomiting in a delayed phase and the results of the nausea endpoints independently were not statistically significant, the agency would like the committee's opinion on whether the data supports the applicant's proposed indication.

The agency would also like comment from the committee regarding the dose of cisplatin considered highly emetogenic. This dose varies in the medical literature**. In the clinical trials that led to the approval of ondansetron, a highly emetogenic dose of cisplatin was greater than 100 milligrams per meter^2. The present ondansetron label describes the

range of 50 to 80 milligrams per meter^2 as a moderate emetogenic dose.

The aprepitant Phase III protocol clearly defined a highly emetogenic dose of cisplatin as greater than or equal to 70 milligrams per meter^2. In spite of this, approximately 20 percent of the patients in these studies received less and were still included in the efficacy analysis.

As part of the submission, the firm included recent literature that defines a highly emetogenic dose of cisplatin as greater than 50 milligrams per meter^2.

The agency performed additional analysis excluding patients who received less than 70 milligrams per meter^2. And the efficacy was maintained for the primary endpoint of complete response in the overall phase as well as the secondary endpoints of complete response in the acute and delayed phases.

The agency's question for the committee is whether any or all of the patients in the Phase III trials received a highly emetogenic dose of cisplatin.

Additional concerns the agency has are related to potential drug-drug interactions that have not been thoroughly evaluated. Aprepitant has a complex metabolic pathway. It has been identified as a substrate, a moderate inhibitor, as well as an inducer of CYP3A4. In addition to this, aprepitant is also an inducer of 2C9.

The proposed treatment regimen states aprepitant may be used in combination with any 5-HT_3 antagonist and a corticosteroid. The applicant has exposure and pharmacokinetic data for only ondansetron and granisetron.

In these drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of the specific drugs in the formulations studied. The agency does not have any data for the intravenous formulation of granisetron or the oral formulation of ondansetron.

Because of first pass metabolism, the inhibitory effect is greatest in the oral formulation. Therefore, one cannot extrapolate PK results from the intravenous ondansetron studies to its oral

formulations.

One needs to consider that oral antiemetics may be utilized as rescue therapy. This could result in higher plasma concentrations of these drugs.

Additionally, within the class of 5-HT_3 antagonists, there are differences in metabolic pathways. Both ondansetron and granisetron are predominantly metabolized by CYP3A4. Dolasetron, however, is metabolized by carbonyl reductase to hydrodolasetron. Further metabolism is then through CYP2D6, 3A4, and flavin monooxygenase.

The agency presently has no data on the use of the aprepitant regimen with dolasetron. This is a concern since it is the only 5-HT_3 antagonist that has QTc and cardiac warnings in its label.

Since dolasetron utilizes different metabolic pathways than ondansetron and granisetron and there are no exposure data on the use of the aprepitant regimen with dolasetron, the agency seeks advice as to whether the regimen proposed in the label should specify only the 5-HT_3 antagonists that have

been studied. Additionally, the agency would like the committee's opinion on whether any additional studies are recommended for dolasetron and/or the oral formulation of ondansetron.

During the Phase III trials, approximately 95 percent of the patients received a concomitant chemotherapeutic agent in addition to the protocol cisplatin. The agency questions whether enough safety data exists to use aprepitant with all chemotherapeutic agents at highly emetogenic doses.

Presently there are no completed PK data available regarding drug-drug interactions of the aprepitant regimen with other chemotherapeutic agents.

The applicant does have an ongoing drug interaction study with docetaxel, which is primarily metabolized through 3A4 pathways. The available data for the five patients enrolled has been reviewed by the agency. The data suggest that the aprepitant regimen has no effect on plasma concentrations of docetaxel.

Aprepitant is a moderate inhibitor of 3A4. The agency would have anticipated some effect on the

metabolism of docetaxel considering the effect the aprepitant regimen had on other drugs evaluated.

The agency questions whether docetaxel is a sensitive enough probe and has concerns as to whether the results of the pending docetaxel study can be used to make generalizations about the safety of the aprepitant regimen with all oncologic agents metabolized through 3A4 pathways.

One well-documented drug-drug interaction was identified during the development of aprepitant. During the Phase IIb trials, an interaction with dexamethasone was identified. This ultimately **led to the sponsor redefining the aprepitant regimen for the Phase III trials and resulted in a decrease in the dexamethasone dose by 50 percent in the aprepitant group.

Similar drug-drug interaction studies have not been completed with chemotherapeutic agents metabolized through 3A4 pathways. This will be discussed in further detail during the biopharmaceutical presentation.

During the Phase III trials, in addition

to the protocol cisplatin, 517 patients were treated with a concomitant chemotherapy metabolized through 3A4 pathways. In spite of the number of patients, there is only limited safety data on most 3A4-metabolized agents.

Common agents known to be 3A4 substrates are listed here along with the number of patients that received them. Of these, the applicant has no safety data for irinotecan or imatinib and has only very limited information on several others. Although specific PK data is not available for any of these, there is reasonable exposure data for paclitaxel, vinorelbine, and etoposide.

Overall, the incidence of adverse events was similar between treatment groups in patients receiving 3A4-metabolized chemotherapy. However, when analysis was performed of serious adverse events by body system, a higher incidence of hematologic and infection-related adverse events was seen in the aprepitant group during cycle 1.

In the aprepitant group, septic shock was reported in three patients, sepsis in one patient, and

a serious upper respiratory infection in one patient. In the corresponding standard therapy group, there were no reports of these serious adverse events.

Neutropenia was reported as a serious adverse event in eight patients receiving the aprepitant regimen compared to only two patients in the standard therapy group. The incidence of anemia and thrombocytopenia were similar between treatment groups.

It is worth noting that during the multi-cycle extension, the incidence of hematologic serious adverse events appear to be similar between the treatment groups. The applicant did perform additional safety analysis broken down by concomitant chemotherapy for the most common agents used during the Phase III trials.

In order to focus on the primary concerns, the remainder of this presentation will address serious adverse events in patients who received concomitant chemotherapy metabolized through 3A4 pathways.

Going in order by number of patients

exposed, the first agent we will discuss is etoposide, which is a 3A4 substrate. During the Phase III trials, 197 patients received etoposide in combination with cisplatin. This breaks down to 106 patients in the aprepitant group and 91 patients in the standard therapy group.

Overall, the incidence of serious adverse events in this population was similar between treatment groups, occurring in approximately 15 percent of the patients.

By analyzing the distribution of these adverse events by body system, it was noted that three times as many serious hematologic adverse events occurred in the aprepitant group.

Neutropenia, thrombocytopenia, and anemia were reported as serious adverse events only in the aprepitant group. When you include both serious and non-serious infection-related adverse events, there were more than twice as many patients reporting an infection in the aprepitant group. Eighteen percent of the patients in the aprepitant group developed an infection compared to nine percent in the standard

therapy group. Furthermore, only patients in the aprepitant group reported serious infection-related adverse events.

The agency is concerned over this trend. However, the numbers of patients are too small to establish any conclusions.

The next most common 3A4-metabolized agent was vinorelbine. A total of 158 patients were treated with this in combination with cisplatin. The incidence of serious adverse events was higher in the aprepitant group than the standard therapy group.

Overall, the incidence of serious hematologic adverse events was similar in both treatment groups. However, serious infection-related adverse events were higher in the aprepitant group. Four patients in the aprepitant group were described as having a serious infection compared to two in the standard therapy group. There were three reported cases of sepsis or septic shock as serious adverse events, and all occurred in the aprepitant group.

On further analysis, there was a marked difference in the incidence of serious

respiratory-related adverse events. Six of the 82 patients in the aprepitant group compared to only one of the 76 patients receiving standard therapy experienced a respiratory-related serious adverse event.

There were no patients in the standard therapy group who experienced respiratory insufficiency; whereas, four patients receiving the aprepitant regimen developed a fatal respiratory insufficiency. In addition to these four fatalities, *three deaths occurred in this subpopulation of the aprepitant group. Two patients died from septic shock and one from cardiopulmonary arrest.

In the corresponding standard therapy group, there were only two fatalities reported. One patient died as a result of a pulmonary emboli. And the other patient's cause of death was reported as unknown.

Vinorelbine is known to have pulmonary toxicity. The agency has concerns that the aprepitant regimen may have affected this toxicity since all fatal cases of respiratory insufficiency occurred in

the aprepitant group. The regimen may also increase the risk of serious infections in patients receiving vinorelbine. However, the numbers are too small to draw any definite conclusions.

The next most common 3A4-metabolized chemotherapeutic agent was paclitaxel. A total of 110 patients were treated with paclitaxel in combination with cisplatin. On analyzing the data, there was little difference between treatment groups for hematologic or infection-related adverse events.

The remaining chemotherapeutic agents characterized as 3A4 substrates either had no or too few patients to permit meaningful analysis. This is a concern for the agency because of potential drug-drug interactions. And the proposed label offers little guidance to the prescribing physicians.

Under the "Precautions" section of the label, the applicant states, "EMEND should be used with caution in patients receiving concomitant medicinal products that are primarily metabolized through CYP3A4. Some chemotherapy agents are metabolized by CYP3A4."

The agency would like the committee's opinion on whether the present safety data is adequate and whether any additional drug-drug interaction studies should be performed since several of the chemotherapeutic agents had too few patients to establish a safety profile.

To better understand the agency's concerns, the Office of Biopharmaceutics will present their findings now. And then we will have questions.

DR. JARUGULA: Thank you, Dr. Dalle'Zanna.

BIOPHARMACOLOGY SUMMARY

DR. JARUGULA: Good morning. I am Venkat Jarugula, clinical pharmacology and biopharmaceutics reviewer of the nda. Dr. Myong Jin Kim of my division has also been doing giant review with me of this NDA.

This morning the sponsor has already discussed the pharmacological properties of aprepitant. So I am not going to repeat this. For the next 20 minutes, I am going to present on drug interactions of aprepitant.

My presentation is divided into the following. First I will give a brief introduction on

the metabolism of aprepitant. Then I will present the results of key drug interaction studies that demonstrate aprepitant as a CYP3A4 inhibitor and then discuss the effect of other drugs on aprepitant followed by drug interactions with 5-HT_3 antagonists. Then I will discuss the most important issue, the potential of aprepitant to interact with chemotherapy agents that are metabolized by CYP3A4, followed by my conclusions.

Aprepitant is extensively metabolized in humans, primarily by oxidation by CYP3A4 isozyme. Based on the *in vitro* and *in vivo* studies, aprepitant regimen is shown to inhibit CYP3A4 as early as one hour after drug administration on day one. Aprepitant regimen induces CYP2C9 isozyme.

Upon multiple dose administration for more than two weeks, aprepitant induces its own metabolism by autoinduction. This phenomenon is not relevant for the current indication. However, this may be important for chronic administration of aprepitant.

Next slide. This slide shows the effect of aprepitant on various CYP3A4 substrates. The AUC

ratio of the CYP3A4 substrate with and without concomitant administration of aprepitant is given in this chart. For comparison, the AUC ratio of control is given as one.

As can be seen here, the aprepitant regimen significantly inhibited the metabolism of midazolam, which is a sensitive CYP3A4 substrate. As can be seen here, the aprepitant regimen significantly inhibited the metabolism of midazolam, a sensitive CYP3A4 substrate, resulting in a 3.34 increase in AUC on day five of aprepitant regimen.

Dexamethasone, as you see, also was increased by 2.24 of this interaction. Sponsor has reduced the dose of dexamethasone in clinical studies by half the drug standard regimen for chemotherapy-induced nausea and vomiting.

The diltiazem, as you see, also was increased by 1.74. Methylprednisolone, also a CYP3A4 substrate, when administered after all administration with aprepitant, diltiazem is a significantly higher AUC change of 2.54 compared to its IV administration of 1.344. This interaction suggests that aprepitant

as a CYP3A4 inhibitor has less effect on IV-administered drugs compared to the oral-administered drugs.

Based on these interactions, the sponsor has, in fact, recommended in the proposed package insert that the IV dose of methylprednisolone be reduced by 25 percent and the oral dose of methylprednisolone be reduced by 50 percent when co-administered with aprepitant.

Next slide. This just shows the effect of CYP3A4 inhibitors or inducers on aprepitant. Again, the AUC ratio of aprepitant with or without concomitantly administered CYP3A4 drug is shown here.

Ketoconazole, an important CYP3A4 inhibitor, significantly increased AUC of aprepitant by five-fold while diltiazem, a moderate CYP3A4 inhibitor, resulted in an increase of two-fold change in the AUC of aprepitant.

Dexamethasone resulted in a modest increase of 30 percent in AUC. On the other hand, rifampin, an important CYP3A4 inducer, resulted in production of almost an 11-fold change in AUC of

aprepitant.

It should be noted that these drugs are not a part of aprepitant's regimen, and the sponsor included a caution in the label when these drugs are to be co-administered.

The other significant drug interactions of aprepitant, aprepitant regimen reduces the S-warfarin. And the INR also is reduced by aprepitant. Therefore, the patients on warfarin need to be monitored carefully when aprepitant is co-administered with warfarin.

Upon multiple dosing for two weeks, the aprepitant reduces the level of ethinyl estradiol by 40 percent and reduces the efficacy of oral contraceptive. This interaction is relevant for the current application of aprepitant. However, since the aprepitant regimen for three days is not studied, sponsor has appropriately recommended in the label to use a backup contraceptive method for a woman.

Many chemotherapy agents are substrates for P-glycoprotein transporter. Aprepitant regimen does not significantly affect the P-glycoprotein

transporter as there is no effect on the pharmacokinetics of digoxin, which is a P-gp substrate. Therefore, aprepitant regimen is not likely to interact with chemotherapy agents via the P-gb transporter mechanism.

The drug interactions with 5-HT_3 antagonists, two pharmacokinetic drug interactions were conducted. These studies showed that aprepitant does not significantly affect the pharmacokinetics of IV ondansetron and oral granisetron. However, there is no data on PK drug interaction with oral ondansetron.

In general, the pharmacokinetic interaction with oral administration of drugs is greater than intravenous administration, mainly because of the inhibition of the dose effect involved in oral administration. However, the package insert for ondansetron states that "This drug is metabolized by multiple p450 isozymes. Therefore, significant drug interactions are not likely."

Furthermore, there is no PK drug interaction data with dolasetron. It is reported that

dolasetron is metabolized by multiple metabolic pathways with carbonyl reductase and CYP2D6 being the main pathways. And CYP3A4 plays a minor role.

Therefore, the pharmacokinetic interaction with dolasetron is not likely. However, as Dr. Della'Zanna mentioned, there is no clinical safety data on co-administration of aprepitant with dolasetron.

Coming to the most important issue today, the potential of aprepitant to interact with chemotherapy drugs metabolized by CYP3A4. As mentioned previously, aprepitant is a moderate CYP3A4 inhibitor.

Many chemotherapy drugs are known to be metabolized by CYP3A4. And, therefore, concomitant administration of aprepitant may increase the systemic exposure to these chemotherapy agents and may result in serious or life-threatening toxicity.

Next slide. The NDA does not consist of any control drug-drug interaction studies with these chemotherapy agents except an ongoing study with IV docetaxel. Although many chemotherapy agents are

known to be metabolized by CYP3A4, there is inadequate information in the literature regarding the role of CYP3A4 in the metabolism and regarding the drug-drug interactions with CYP3A4 inhibitors.

There are two studies reported in the literature with ketoconazole. One study reported that the ketoconazole increases the exposure of SN-38, the active metabolite of irinotecan, by 100 percent.

Another study reported that ketoconazole does not significantly affect the pharmacokinetics of paclitaxel as this drug is metabolized by multiple pathways. This result is consistent with the lack of safety signal noted by Dr. Della'Zanna in the safety database of the NDA for patients who are on paclitaxel.

As Dr. Della'Zanna also discussed, there is some safety data available in the NDA for patients who are on etoposide, paclitaxel, and vinorelbine. However, there is minimal or no data available on co-administration of aprepitant with irinotecan, ifosfamide, imatinib, vinblastine, and vincristine, which are also known to be CYP3A4 substrates.

As mentioned previously, there is a drug interaction study ongoing with IV docetaxel. The primary data on five patients show no interaction with docetaxel.

Since the docetaxel is known to be metabolized by CYP3A4, it is rather surprising to see no effect of aprepitant on docetaxel. Therefore, the interaction results of docetaxel may not be generalized to other chemotherapy agents.

As mentioned previously, the sponsor's proposed package insert in the "Precautions" section states that "EMEND should be used with caution in patients receiving concomitant medicinal products that are metabolized through CYP3A4. Some chemotherapy agents are metabolized by CYP3A4."

However, the label does not list these chemotherapy agents, and the NDA does not contain any information or data to provide dosage adjustment or appropriate caution when aprepitant is co-administered with these chemotherapy agents.

Conclusions. Aprepitant is extensively metabolized in humans, primarily by a CYP3A4 isozyme.

Potent inhibitors increase the aprepitant exposure significantly. Potent inducers reduce the aprepitant exposure significantly. And based on the drug-drug interaction studies, aprepitant is known to inhibit the CYP3A4 metabolism of the co-administered drugs.

Co-administration of aprepitant with the chemotherapy agents that are metabolized by CYP3A4 may increase the exposure to these agents and may result in serious or life-threatening toxicity.

Finally, the potential of aprepitant to interact with the chemotherapy drugs that are metabolized by CYP3A4 has not been characterized adequately.

This concludes my presentation. Thank you very much for your attention.

CHAIRPERSON CAMILLERI: Thank you, Dr. Della'Zanna and Dr. Jarugula. Maybe you should both be at the microphone now to address questions from the committee members pertaining to your presentations. Dr. Kelsen?

QUESTIONS ON PRESENTATIONS

DR. KELSEN: Well, I thank you for that

review. I think the point we were discussing a few minutes ago is that, is there a chance that the antiemetic will affect outcome from the therapy?

I think there are two sides to that. You have discussed toxicity. I guess I would just make the comment that, unfortunately, there is not a direct correlation between therapeutic efficacy and toxicity with many chemotherapeutic agents. That is, not all patients who have serious toxicity also have an excellent response.

The MTDs are developed because that is the maximum dose that you can give. But making assumptions that because you don't see much more in the toxicity, you, therefore, will see equal efficacy**, that may not be a direct correlation.

CHAIRPERSON CAMILLERI: In fact, wasn't the analogy that since there wasn't less toxicity, there should be similar therapeutic efficacy?

DR. KELSEN: Yes. I guess what I am trying to say is that I do understand the hypothesis, but I think that's a hypothesis, hasn't been proven.

I also am aware that it is not usual to

look at therapeutic endpoints with antiemetics, but the reason I asked that before is that many antiemetics don't apparently have this degree of drug-drug interaction. So I think it is a little bit of a different situation.

CHAIRPERSON CAMILLERI: Dr. LaMont?

DR. LaMONT: Yes. I wonder if there was a clustering in the same patients of infectious adverse events and neutropenia or can you tell if these are separate or the same patients?

DR. DELLA'ZANNA: I'm not sure from the data that I have right now. I don't know if the firm would have any input on that, if that was clustered together.

DR. REINES: Seven eighty-seven, please. Okay. So this is the infections in the total population in Phase III, cycle 1. And, as you can see, most of the infections are not neutropenic infections, either in the aprepitant or in the control regimen.

CHAIRPERSON CAMILLERI: Dr. Levine?

DR. LEVINE: Just to follow up that slide

and Dr. LaMont's question. It's of interest in very large studies in hepatitis, interferon causes neutropenia, but it doesn't seem to be causing a correlation with infection very often.

There is a disconnect because if one looks at the individual white count and then go down to neutrophils percentage and then go down to the absolute neutrophils, there is a much better correlation.

So I wondered perhaps later at a time -- you probably don't have that data -- whether the absolute neutrophil count, the percent in the absolute neutrophil count, was, in fact, a disconnect, as opposed to the data you showed. But it is interesting that that large data didn't seem to show a very good correlation either.

DR. DELLA'ZANNA: Well, one of the concerns the agency has wasn't necessarily related specifically to the incidence of serious adverse events as much as the incidence of serious adverse events for specific chemotherapeutic agents.

We realize that the numbers that we were

talking about were small and the differences were small. But when you broke them down specifically -- for example, can you go to slide 16?

Etoposide. Overall, the incidence of serious adverse events was identical, but when you looked at them specifically for neutropenia, there were three times as many. The results that the firm has presented have been serious adverse events overall inclusive of both CYP3A4 and non-CYP3A4 or CYP3A4s completely inclusive.

Now, like paclitaxel, we saw no difference at all in either hematologic or infection-related adverse events. So I don't think we can look at them as a broad class and say, "All CYP3A4 chemotherapeutic agents are going to have the same safety profile."

And that was one of the other reasons I emphasized and pointed out that the docetaxel study may not be something that we can rest a lot of our faith on because it had absolutely no effect on plasma levels.

I would have anticipated at least a minimal effect, something that we could have at least

seen as a normal comparison. I think we would have predicted approximately like a 15 percent effect.

CHAIRPERSON CAMILLERI: Dr. Brawley?

DR. BRAWLEY: Out of some ignorance, aren't we dealing here not just with different drugs but also with different polymorphisms of CYP? I mean, so that is an entirely different variable.

DR. DELLA'ZANNA: Right.

CHAIRPERSON CAMILLERI: Did you want to expand on the inference from your comment?

DR. BRAWLEY: Well, I'm wondering if we need to try to look at I guess if I were to put it into a simple question, are there perhaps populations that I would define, not necessarily by race, maybe even area of geographic origin, but define by the polymorphism of the p450 that they have who might be dosed very differently with this drug or with some of the other drugs that we are using.

DR. JARUGULA: To address the polymorphism, in general among the CYP 450 isozymes, the isozymes 2B6 and 2C9 are known to have extensive polymorphisms. They are poor metabolizers and tend to

be metabolizers.

There may be some information in the literature coming up recently on the polymorphisms of various CYP3A components, but we don't have a good handle I think on the polymorphisms of CYP3A, and this drug is mainly metabolized by CYP3A4.

Among the components that are to be given with the aprepitant which are corticosteroid, dexamethasone, and 5-HT_3 antagonist ondansetron, these, specifically 5-HT_3 antagonists, are less prone to drug-drug interactions because they have multiple metabolic pathways.

So I am not sure if there is any more information that can be added to address the issue of the polymorphism.

CHAIRPERSON CAMILLERI: Dr. Metz?

DR. METZ: Yes. Thank you.

One of the questions that FDA has asked us to look into is whether we think all 5-HT_3 drugs in the class should be considered the same, but after your presentation, my understanding is that you would be less concerned with dolasetron than you would with

the other two 5-HT_3's. Can you confirm that? That is question number one.

Question number two relates to anti-fungal agents. I think many of these patients develop thrush, for example, and end up getting anti-fungals. Nobody has actually raised this as a specific concern, but I am wondering if you think that should be something that should be looked at carefully.

DR. JARUGULA: Regarding the first question, the interaction with dolasetron, based on its multiple metabolic pathways, we don't think that there will be a significant pharmacokinetic interaction. However, there could be a pharmacodynamic interaction or there could be a different safety profile when aprepitant is administered with the dolasetron, specifically as Dr. Della'Zanna mentioned. Dolasetron is known to have QT prolongation and other cardiac side effects.

Regarding the second question about anti-fungal agents, ketoconazole, which is an important CYP3A4 inhibitor, actually significantly reduced the AUC of aprepitant by about five-fold.

That is quite a bit of significant interaction, and it is a concern that needs to be brought out properly or adequately in the label.

CHAIRPERSON CAMILLERI: Dr. Metz, is it fair to say that the fungal infections don't usually happen in the first couple of days?

DR. METZ: I have thought about that, but the truth is we have got to realize these patients are going through multiple cycles of chemotherapy and are going to be getting repetitive regimens. And you can certainly pick up your fungal infection in an intervening period and come up for chemo in due course.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Fogel?

DR. FOGEL: I also have a question related to the ketoconazole. The ketoconazole is a very potent inhibitor of the 3A4 enzyme, actually much more potent than aprepitant. Do you have any data on ketoconazole effects on chemotherapeutic agents?

DR. JARUGULA: As I presented in one of my slides, there are two studies reported with

ketoconazole. One study showed that the ketoconazole increases the AUC of the irinotecan active metabolite by 100 percent. And the other study showed that ketoconazole does not affect the PK of paclitaxel. These are the two studies we have come across with the chemotherapy agents with ketoconazole.

DR. FOGEL: Can we use ketoconazole as a surrogate for aprepitant effects?

DR. JARUGULA: The problem in using ketoconazole as a surrogate is that midazolam is a sensitive CYP3A4 substrate for measuring these interactions.

If you compare the interaction with midazolam for ketoconazole and the aprepitant, aprepitant only results in a 3.34 change in AUC. But ketoconazole can go up to a 16-fold change in AUC.

But, again, with chemotherapy agents, depending on the sensitivity of those agents to the CYP3A4 isozyme, a change of two-fold or even less than two-fold could be concerning in terms of its toxicity.

So there is not adequate information in the literature to say or to rank these chemotherapy

agents in terms of their metabolism by CYP3A4. So that is a difficulty unless you study with main chemotherapy agents that are known to be metabolized by CYP3A4. I would think that you may not be able to credit the interaction.

CHAIRPERSON CAMILLERI: Dr. McLeod?

DR. McLEOD: I'm trying to solidify opinion on how much we should care about the drug interactions in terms of the change in blood levels of the aprepitant and not its effect on other drugs but, rather, its change in blood levels.

Some of the data that was presented, we tried to get this out from Dr. Petty during the discussion, but there seems to be a fairly wide index, a therapeutic index, with this agent.

I wondered, with your review of the data, which is obviously more extensive than you are able to present during the short presentation time here, whether you had a feel for whether even a doubling or a halving of blood level would likely change the place a patient would be on that sigmoidal affect curve that was demonstrated during the applicant's presentation.

DR. JARUGULA: Yes. Regarding the dose-response of the aprepitant, sponsor has investigated three dose regimens, 40/25, 125/85, and 375/250. Based on the trough concentrations that you can expect from these dose regimens, you don't expect a significant improvement in efficacy, going from 125/85 to 375/250.

The efficacy is almost maxxed out at 125/85 regimen if that is your question. I can see where you're coming from there, but if you are using rifampin or something like that.

If your blood levels were decreasing, were cut in half, for example, I don't have a feel from reading the data that was provided to us whether that is likely for the efficacy to fall off the curve at that point. You know, there was a sigmoidal curve, and there is quite a lot of variability shown, at least with the standard deviation.

DR. McLEOD: How about in the other direction?

DR. JARUGULA: As far as I know, in the dose-ranging studies, I think that's the only place

where they have tested multiple dosage regimens. And in the Phase III, only one dosage regimen was tested.

For the lowest dose regimen, 40 milligrams, 25 milligrams, the sponsor reported that the efficacy was not maximal. However, it was shown to be efficacious. But it was not at the maximal response that you hope for.

CHAIRPERSON CAMILLERI: Dr. Desta?

DR. JARUGULA: But regarding how much lowering of plasma levels would interfere with the efficacy, certainly rifampin reduced the **blood levels by 11-fold. And that is a lot of change in the blood levels. The efficacy I think would be affected.

DR. DESTA: In most of the presentations, three of four is mentioned. I never heard about three of five. And that is polymorphic, actually. It could also influence the drug interaction profoundly. It could also influence some of the pharmacokinetics. That is one question for the company and for you guys.

The second question is you mentioned that dolasetron has multiple metabolites. And you would not expect any drug interaction with the aprepitant.

Is that correct?

DR. JARUGULA: Yes, that is correct.

DR. DESTA: Yes. If you have, for example, a poor metabolizer which is not producing any enzyme 2B6 because it seems that 2B6 is the enzyme which is metabolizing the active modifier by the carbonyl reductase, then if you put on top of that like aprepitant, wouldn't you expect any significant drug interaction in that respect?

DR. JARUGULA: If that main metabolic pathway is shunted to a different metabolic pathway, which is 2C8, it is possible that you could see an interaction with aprepitant. It is possible.

CHAIRPERSON CAMILLERI: Is that a question about 3A5?

DR. JARUGULA: The question regarding 3A5, in the NDA data package, I haven't seen any information on CYP3A5 isozymes specifically. If sponsor has anything more to add, I don't know.

CHAIRPERSON CAMILLERI: Ms. Hoffman?

MS. HOFFMAN: I guess my question was fairly similar. I just wondered if there was data

looking at further downstream mechanism, molecular mechanisms, and then potential drug-drug interactions from the downstream molecular changes as well.

DR. JARUGULA: That's a good question. As alluded to in the presentation, aprepitant on chronic administration induces its own metabolism. And there is a conclusion in the NDA that aprepitant induces CYP3A4 isozyme also.

So that could lead to a different scenario of interactions where aprepitant might induce the metabolism of the co-administered drugs and result in lower efficacy if it is administered chronically. So that is a significant issue when this drug is going to be considered for the chronic administration.

CHAIRPERSON CAMILLERI: Dr. Proschan?

DR. PROSCHAN: Yes. You mentioned the multiplicity issue with respect to some of the secondary outcomes, nausea being one of them. It seems to me that there is a big multiplicity issue with the adverse events as well, namely you are looking at many different drugs, many different organ systems. It seems like it would be pretty likely that

you would find one of them with a nine to three difference.

DR. DELLA'ZANNA: Right. We are not playing that down, and we realize the numbers that we are talking about and the differences that we are talking about are small.

However, we are concerned that we don't have enough information to draw a conclusion, and we have to work with the numbers that we have.

CHAIRPERSON CAMILLERI: Dr. Cryer?

DR. CRYER: One of the things that caught my attention from the sponsor's presentation was this difference in adverse event rates in the multiple-cycle extension versus just cycle 1. And most of the data that you showed us with respect to the adverse events were from cycle 1.

I was wondering what sorts of patterns you might have observed with respect to cycles 2 through 6 with specific regards to the adverse events.

DR. DELLA'ZANNA: The serious adverse events balanced out a little more during the multi-cycle extension. Okay? But one of the concerns

I had regarding, for example, like vinorelbine, we had a fair number of pulmonary problems that occurred. And if you removed those patients from the multi-cycle extension, then the number of patients exposed is also smaller.

Overall, most of the things they focused on which were the greatest differences were during the cycle 1.

DR. CRYER: In follow-up to that, I would like to follow up with the sponsor for that specific question. So I believe, Dr. Reines, on the very last slide which you showed us that had to do with infections during cycle 1, I don't remember the specific number, but it was the last one that you requested to be shown, that was cycle 1 data. Would you happen to have similar data for cycles 2 through 6 with respect to infection?

DR. DELLA'ZANNA: Can I just clarify one of my concerns, too, which may not be able to be demonstrated on that slide? The slide that we are going to see is maybe multi-cycle extension data, but it is not broken down specifically to the areas of

concern that the agency has, which are specifically the individual CYP3A4 chemotherapeutic agents.

Overall I tried to include that in my presentation, that overall the incidence of serious adverse events as a whole was similar between the two treatment groups. It's only when we broke these out and looked at the specific chemotherapeutic agents that we started seeing some small but definite differences. These differences are where we are focused on concerns.

If we see another slide that shows that overall in cycle 2 through 6 that the serious adverse events were the same, I don't think it's going to answer the agency's concerns.

DR. REINES: I don't think I have that same breakdown of infections, but I can show the serious adverse events that occurred. If I could have 509, please? If we look at serious adverse events over multiple cycles, the incidences were very similar between the two treatment groups. And the more common are indicated on this slide.

CHAIRPERSON CAMILLERI: Okay. Perhaps

just for clarification, Dr. Della'Zanna, can you tell us a little bit more about the vinorelbine pulmonary toxicity that concerns you? The specific question I have is, is it just conceivable that there were more people with lung cancer in the aprepitant group relative to the control arm?

DR. DELLA'ZANNA: Overall the incidence of cancers was pretty well-balanced within each group. So to say that this population had a higher prevalence of lung cancer that would have resulted in this bias I don't think was what occurred.

CHAIRPERSON CAMILLERI: Can the sponsor specifically answer that question? Among the people with pulmonary or respiratory problems in the vinorelbine-treated group, were there more in the aprepitant group who happened, for instance, to have been lung cancer patients than in the other group?

DR. DELLA'ZANNA: Most of the serious respiratory or fatal respiratory insufficiencies occurred at the same site. So I am not sure as far as the numbers specifically for the balance of vinorelbine for lung cancers.

DR. REINES: Could I talk about those patients, the vinorelbine patients, for just a moment? I want to emphasize that myelosuppression is the dose-limiting toxicity with this agent and that we did not see an excess there.

In terms of the patients with respiratory insufficiency, these did occur at one site, as was mentioned. At this site, we specifically spoke with the investigator. These were all patients with lung cancer, although there was not an imbalance of lung cancer between the aprepitant and control groups.

However, these patients did not have the respiratory insufficiency typical of vinorelbine; that is, the acute dyspnea that occurs within a day or two. These were chronic patients. And the investigator said they died of their lung cancer. They did not have any sort of bronchospasm or acute dyspnea.

CHAIRPERSON CAMILLERI: Dr. Brawley, did you have a question? Go ahead, Mike.

DR. PROSCHAN: I had a question on a different topic. I don't know if it is appropriate, but it was about the nausea. The rescue medication,

is that something that is given at the time someone is feeling nauseous? Is it given like if I am nauseous today, I get it and then two days later, I get it again if I am nauseous again or is it given from then on?

DR. DELLA'ZANNA: No. The rescue medication was administered upon complaints of nausea. It wasn't something that was scheduled. As a matter of fact, the firm actually while still blinded analyzed the use of "rescue medication" to make sure that it was appropriately given. And they did a good job isolating those patients out to make sure that it wasn't just given prophylactically where somebody said, "Oh, I might get nauseous."

DR. PROSCHAN: It sounds like there are a fair number of people who got rescue medication and checked or put a mark that is less than five on that VAS score. I am wondering if they just didn't remember. I mean, they had to be rescued from something. Maybe they didn't know that even if you don't vomit, you could be nauseous.

DR. HORGAN: Right. We were very careful

about the instructions that we proffered the patients. I think one of the key issues that one has to bear in mind and that maybe didn't come out in my presentation is emesis is easy.

The patients had a diary. They recorded the emetic event. When they took rescue, they recorded the time of the rescue event. Nausea is from one's own personal experience a much different entity. The patients were taking daily ratings of their nausea experience over the preceding 24 hours. And so the correlation between their actual experience of nausea on a given day is different than it was for the other efficacy elements: emesis and rescue.

We did look carefully to corroborate the fact that the patients were actually taking rescue for nausea. And we saw that the patients that took rescue did, in fact, have higher nausea ratings than the patients who did not take rescue. So we are confident that it was an effective surrogate of the experience of nausea for the patients.

Does that address your question adequately?

DR. PROSCHAN: Yes.

CHAIRPERSON CAMILLERI: Ms. Cohen?

MS. COHEN: Maybe you already presented it, but how often did people in your clinical trials have to take rescue medication as a percentage?

DR. HORGAN: We presented the data in my presentation that actually showed the percentage of patients who took rescue at least once. That was a component of our primary endpoint. So we had approximately 20 to 25 percent of the patients in both of the Phase III trials took rescue at some point.

MS. COHEN: Did you delineate between one, two, three, or four or just --

DR. HORGAN: For the purposes of the primary endpoint, we did not, but we did enumerate all of the occurrences of rescue therapy. And we saw that consistently the patients in the control group were taking more rescue. They were taking rescue more frequently than the patients in the aprepitant treatment group.

CHAIRPERSON CAMILLERI: Do the committee members have any other questions?

(No response.)

CHAIRPERSON CAMILLERI: If not, this is a good time for us to take a break. We plan to be here again at 1:10 so that we can start the proceedings for the afternoon. Thank you very much.

(Whereupon, at 12:15 p.m., the foregoing matter was recessed for lunch, to reconvene at 1:10 p.m. the same day.)

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

(1:12 p.m.)

OPEN PUBLIC HEARING

CHAIRPERSON CAMILLERI: Okay. Good afternoon. We are now at the stage in the proceedings where we would invite the open public hearing or presentation. And we have not yet received any notification of such a presentation. Is there anybody from the public that wishes to make such a presentation at this time?

(No response.)

CHAIRPERSON CAMILLERI: If not, I think we should move on to the next item. Really, it is to ask Dr. Justice to address the committee and give us the charge.

CHARGE TO THE COMMITTEE

DR. JUSTICE: Well, our charge to the committee really is brief. And, as I discussed this morning, now that you have heard the presentations, we would appreciate your discussion and vote on those questions.

As you can tell from the questions and the

presentations, we are particularly concerned about the potential for drug-drug interactions, particularly with chemotherapy drugs that are metabolized by CYP3A4.

So that is basically all I want to say. I think we can move to the committee's discussion of the questions and votes.

CHAIRPERSON CAMILLERI: Thank you very much. Are we going to present the questions or are they on a slide?

DR. JUSTICE: They are on a slide and in your handouts, I think, as well.

CHAIRPERSON CAMILLERI: Okay. Just to remind the committee members, as we address each question, if there are areas of clarification where we still wish perhaps the sponsor to give us some further information for clarification, I think we still have an opportunity to do so.

Also, we will need to go around the table. And each individual member of the committee will be asked to give a vote yes or no. If I forget to specify your name before you give your vote, please

remember to give your name so that it is there for the record.

Okay. The first question, has the aprepitant regimen been demonstrated to be effective in the prevention of nausea and vomiting in the acute phase and in the delayed phase?

I guess the first thing I need to ask is are members around the committee wishing to have some further clarification on any of these issues? Dr. McLeod?

DISCUSSION OF QUESTIONS

DR. McLEOD: I think one of the issues that has come up is the issue of effectiveness against vomiting versus effectiveness against nausea.

I would like some further clarification of this because the question that is going to be posed to us includes both. And so I wouldn't want to have to err on one side or the other without being clear if we can divide the question or at least understand specifically what is on the table there.

CHAIRPERSON CAMILLERI: Okay. I think we are going to have some restricted time for some

clarification from the sponsor with regard to the specific point.

DR. HORGAN: I think it's compellingly clear that our data shows that we have efficacy in the prevention of both nausea and vomiting with our primary endpoint. I would like to show slide 96, the primary endpoint of complete response being a patient having no emesis and taking no rescue therapy and highly significant advantages for the aprepitant regimen with the primary endpoint --

DR. HOUN: Okay. I'm not sure where. The question on the table was how we should ask the question should be divided. I am not really sure if people are wanting to go through show us the data again about this before we vote.

May I ask, Dr. McLeod, is it that you are asking in terms of how you should vote? You are questioning whether the "and" phrase, "nausea and vomiting in acute phase," "nausea and vomiting in delayed phase," should it be voted as nausea and vomiting or you were asking whether it should be separated as nausea in the acute phase, vomiting in

the acute phase? Is that your question?

DR. McLEOD: I guess so, yes. I mean, I don't know what the procedure is in this context, but certainly the data for one of those areas is dramatically more compelling than the other.

I didn't know which way we probably are going to vote; either way you want it. But I just wanted clarity that if we have to be **100 percent for both of those indications, then that may sway some of the votes versus whether we disbelieve that it is a good antiemetic, as opposed to anti-nausea, agent.

CHAIRPERSON CAMILLERI: So let me just ask for a clarification from Dr. McLeod. Would it make it easier if the question were posed, is this medication effective for vomiting in the acute phase and the delayed phase? That's one question.

Second question, is this medication effective or have the data been demonstrated that it is effective in the context of nausea in the acute phase and the chronic phase, or the delayed phase?

DR. McLEOD: Yes. I think that's really getting to the gist of what I am trying to ask because

practically speaking, it doesn't matter. You don't treat nausea and vomiting separately. You give therapy for them together.

Going by the data that has been presented, the data is certainly much stronger for vomiting than it is for nausea.

CHAIRPERSON CAMILLERI: I actually think that I am trying to understand how that can be clarified further by data that the sponsor may have. I think there has been ample opportunity to tell us what the primary endpoint is.

I guess what the people around the table might need to decide for themselves is whether the complete response in the lack of use of antiemetic medication safety constitutes a surrogate for the symptom of nausea.

I think that is what it comes down to ultimately because the nausea, no significant nausea and no nausea demonstrated by the VAS of -25 or up to 5, the data had been presented. And I don't think that it will be useful to present them again.

Is that clear?

DR. ERB: I do think that there is an opportunity here to clarify a little bit more on the nausea and response, too, to the impact on patients' lives, which I think is an equally important measure that has not been presented so far.

CHAIRPERSON CAMILLERI: Okay. Dr. Horgan, let's have two minutes with one pivotal slide to convince us more than what we have just addressed here?

DR. HORGAN: Well, I think that the single slide that I would like to show is slide 203, which just emphasizes that for the data that we collected, the continuous variable of nausea over the entire spectrum, maximum nausea ratings, we saw a consistent advantage for aprepitant, which was statistically significant. The data was similar for both the individual studies and was statistically significant from one of those studies.

So, in addition to the data that I have shown for this particularly troubling symptom, we also had data assessing the impact of nausea and vomiting on patients' daily lives.

Now, the committee hasn't seen that data, but I think that provides compelling additional information that illustrates the consistency of the effect that we saw in the prevention of nausea. And also it provides information on the clinical significance of the effects that we saw.

So I think that it may be valuable to see for the committee to have an opportunity to see that data. My colleague can present that.

CHAIRPERSON CAMILLERI: I think that it probably isn't necessary at this stage. Thank you very much.

I think we can go back to Dr. Houn's question.

DR. HOUN: I think that if you do want to split them out, you can, but we would want you to vote also on this question, the combined.

CHAIRPERSON CAMILLERI: That's fine. We can certainly address the question. Are there any specific questions or questions of further clarification pertinent to question number 1 that the members of the committee wanted to address? Dr. Metz?

DR. METZ: Yes. I think we need to define the regimen because that comes up in later questions, but when you say, "Has their regimen been demonstrated?" that is the study drug regimen used in each of these pivotal trials, one with granisetron, one with ondansetron. Is that correct?

DR. JUSTICE: That's correct.

DR. LaMONT: Yes. I would like to hear from the clinical oncologists about the separating out of these symptoms because it seems to me that they are virtually inseparable.

DR. JUSTICE: I think there is not a significant difference.

DR. BRAWLEY: I see perhaps some more of a difference than Dr. Kelsen, but I read this really as more of a quality of life question. I would just say, has the regimen been demonstrated to be effective in improving the quality of life in the acute phase and in the delayed phase?

CHAIRPERSON CAMILLERI: So I think that the consensus is that we put these back together again. And that is the question the agency really

wants us to answer.

Are there any other issues of clarification before we start to take votes? Ms. Cohen?

MS. COHEN: I think that you said that less than 25 percent of rescue therapy was used; is that correct, when I asked before?

DR. HORGAN: Yes. Approximately 25 percent of patients used rescue therapy.

MS. COHEN: Can I say something? You know, a lot of you are delivering physicians. And you have to deal with the anguish of people having nausea and having vomiting.

As a consumer member, I think there is another dimension that we need to be protected also. And I think since you have to deal with the end result of very sick people, your compassion is very strong. I would like to know that there is a balance here in the drug-drug reaction. And not studying it, to me, I am very concerned.

And that is my speech.

CHAIRPERSON CAMILLERI: Thank you.

Other issues related to question number 1 or are we prepared to go around the table and answer the question? Michael?

DR. PROSCHAN: So the decision was to do two things, the combined and then the nausea separately or just the one thing combined?

CHAIRPERSON CAMILLERI: I think the decision is that we go back to the original question as posed by the agency and address it separately for the acute phase and the delayed phase.

DR. PROSCHAN: So it is just nausea, then? That is the --

CHAIRPERSON CAMILLERI: No. It is the combined package of prevention of nausea and vomiting.

Okay. I think not seeing any other hands coming up or questions being posed, I would like the committee to start taking a vote on this specific issue. So let's just break this up into two bits again just so that we are clear.

The first question is, has the aprepitant regimen been demonstrated to be effective in the prevention of nausea and vomiting in the acute phase?

I am going to start asking Dr. Proschan. Would you give us your vote?

DR. PROSCHAN: I would vote yes.

CHAIRPERSON CAMILLERI: Dr. Desta?

DR. DESTA: I will vote yes.

DR. McLEOD: Howard McLeod. Yes.

DR. BRAWLEY: Otis Brawley. Yes.

DR. KELSEN: Yes.

CHAIRPERSON CAMILLERI: That was Dr. David Kelsen, yes.

DR. LaMONT: LaMont. Yes.

DR. LEVINE: Levine. Yes.

DR. METZ: Metz. Yes.

CHAIRPERSON CAMILLERI: Camilleri. Yes.

DR. CRYER: Cryer. Yes.

DR. FOGEL: Fogel. Yes.

MS. COHEN: Cohen. Yes.

MS. HOFFMAN: Hoffman. Yes.

CHAIRPERSON CAMILLERI: Okay. We can address the second question now or part 2 of question number 1, has the aprepitant regimen been demonstrated to be effective in the prevention of nausea and

vomiting in the delayed phase?

DR. PROSCHAN: We have to vote or is there a discussion of that? Are we at the voting stage on that?

CHAIRPERSON CAMILLERI: I am happy to entertain further discussion. This is a very important point. Thank you, Dr. Proschan.

DR. PROSCHAN: Okay. Yes. I think it is difficult to tell because of the fact that the rescue medication could have saved them or they may have not thought about the fact that the rescue medication meant that they did have nausea. And once they took the medication, they didn't feel that they had it anymore. So I think it is difficult.

The other issue is much cleaner to answer.

CHAIRPERSON CAMILLERI: Can I ask for a clarification perhaps from the agency side? It is my impression that one of the presentations said that rescue medication was used in 28 percent in the control group and 18 percent in the aprepitant group. Is my recollection correct?

DR. DELLA'ZANNA: That's correct. I am

not sure if you are understanding what I was also trying to emphasize. Their complete response in the overall phase as well as acute and delayed phases excluded the use of rescue therapy.

So if you just focus on the primary endpoint as well as the secondary endpoints of complete response, we** are ignoring the use of rescue therapy because they didn't have any.

So I don't have as much of a concern regarding that for the delayed phase because it was statistically significant without the use of rescue therapy and then in support of their findings that the use of rescue therapy now was no longer considered a responder and the patients had failed the primary endpoint, the use of rescue therapy was used more frequently in the standard therapy group.

I don't know if that better answers what you were saying.

DR. PROSCHAN: When you look at whether they had nausea or not, their scores if they had the rescue therapy are likely to be different than their scores if they didn't have the rescue therapy.

So I still think there is a problem. It is certainly much less clean to try and answer that question tan the first question.

CHAIRPERSON CAMILLERI: Other clarifications needed on this point? Yes. Go ahead, Dr. Desta.

DR. DESTA: Yes. I'm not sure whether a single dose or a multiple dose is recommended. I mean, if we see the figure 7-3, it seems that the single dose does it. I don't know whether there is a difference between the 52 and the 43 percent difference in the delayed effect.

So I am not sure about the dosing interval. Is a single dose enough? According to this figure, it seems that a single dose is also doing that.

CHAIRPERSON CAMILLERI: Dr. Cryer is indicating to me that the five-day results are indicated here. And presumably that is what the sponsor is recommending, that this would not just be a one-day treatment, but it would go on for three days.

DR. HORGAN: The Phase III regimen.

CHAIRPERSON CAMILLERI: According to the Phase III regimen.

Maybe I could have a clarification from the agency. Is it possible to answer yes to this question but then to make recommendations on the indication? I think there is some discomfort with regard to the over-encompassing conclusion that there is about nausea here. I think there is a practical discomfort around the committee members.

So is it, in turn, inconsistent or is it still possible to work with a general statement in response to question number 1 but to clarify the implications perhaps clearly in the indication?

DR. JUSTICE: Certainly if you can clarify it, we would appreciate it greatly.

CHAIRPERSON CAMILLERI: Dr. Fogel and then Dr. Levine.

DR. FOGEL: As we are going on, I am getting more and more confused. So I guess my question is for the agency. In this study when the data was presented and then in the initial presentation by the agency, there was agreement that

the delayed phase was effective.

If I understood correctly, there is a significant reduction in the use of rescue therapy in the delayed phase. And, as I have been listening to the discussion, it seems to be revolving around the VAS scores, where there does not seem to be a significant difference. Is that correct?

DR. DELLA'ZANNA: Well, it is a little more than just the VAS scores. Historically we have used and we are concerned about applying an indication that this could be used for nausea. Okay? Independently if you look at that endpoint, it doesn't become significant.

I agree with Dr. Brawley that it is difficult or impossible to separate nausea and vomiting from one another. And I agree in practice that vomiting is the progression of severe nausea. Historically we have to also be concerned with the potential that this could be used as an indication for nausea. And because of that, that is the only reason we separated these out as a question for the committee.

We have similar concerns as far as yes, we agree it was significant in the overall, complete response overall, phase, acute phase, and delayed phase. But if you looked at it independently for nausea, it wasn't as convincing.

The **firm has done a very good job and a good argument stating that the use of rescue therapy is a surrogate for the degree of nausea. We have not used that in the past. And so we are setting a precedent.

DR. FOGEL: The question I have about the nausea scores, it was my understanding from the previous discussion that when people marked their score, it was if they took rescue therapy, they still got to mark a score. Is that correct?

DR. HORGAN: Yes.

DR. FOGEL: And when you calculated the number of people who were less than 5 and less than 25, you did not exclude those who had not already taken rescue therapy.

DR. HORGAN: Absolutely. Every patient in the study was making daily nausea recordings,

irrespective. And that is one of the key issues, that despite the fact that patients in an active control group were taking more rescue therapy, we consistently found an advantage with the aprepitant treatment in our nausea VAS scores.

DR. FOGEL: Did you do a subset analysis? Since you have been slicing the data a number of different ways, did you do a subset analysis where you excluded those who took rescue therapy and just looked at the nausea scores?

DR. HORGAN: We didn't think that was a valid way to look at it from the perspective of the syndrome of chemotherapy-induced nausea and vomiting because there are complex relationships between emesis and nausea or rescue and nausea. So we focused on looking at the total patient population in our assessments of nausea and also rescue therapy, though we did note that rescue therapy was associated with higher nausea scores in general.

CHAIRPERSON CAMILLERI: Dr. Levine?

DR. LEVINE: My question is really for the agency. I think it is marginal, the effects on

nausea, but I think what I am concerned about is in the labeling. I don't have a problem with labeling that might even say "highly emetogenic," but I think if we put the word "nausea" in the label at all eventually, that this drug is for nausea, it may be another subject. But forgetting the off-label possible use, forgetting that it is limited to chemotherapy, I am concerned in that delayed period, that doctors will be looking at what they think is a good drug for nausea. It is that simple.

And I just wondered, are we mandated in any reason? I think it is a sticky wicket to try to get into the word "nausea." I agree with Dr. LaMont. They are linked together in patients. I don't have a problem with that. But I think if it is going to come to putting a label on this with nausea, I would be hesitant about it.

CHAIRPERSON CAMILLERI: Dr. Brawley?

DR. LEVINE: Can they clarify that? Can the company clarify whether this is going to be in the label or not?

DR. HOUN: Well, this is what they are

proposing for labeling. I imagine this is what they desired, nausea and vomiting. They are saying yes. I think we are looking for your recommendations. You know, I think there are safety concerns, as you know, as we will discuss more this afternoon.

I think, actually, if you can help us understand. Our standard is safe and effective as labeled, but that is for approval. But to stay on the market, it is safe and effective as used because drugs run into trouble if they are used inappropriately.

So I am interested in GIs' as well as other docs', cancer docs' opinion on what are the problems we might run into in real use.

CHAIRPERSON CAMILLERI: Dr. Metz?

DR. METZ: Can I just clarify something? My understanding is what the company is asking for is a regimen that is going to be given to people up front who are going to be getting chemotherapy to prevent them from getting chemotherapy-induced nausea and vomiting, which is bad. This affects a lot of people and can be reduced by 20-plus percent with this particular regimen.

Giving PRN drug for nausea in patients who happen to have received chemotherapy beforehand to me is going to ultimately be a big off-label use unrelated to what we are talking about here today. If we talk about chemotherapy-induced nausea and vomiting that you are going to prevent with this regimen, you can't separate the nausea and vomiting. That is the syndrome.

But if you want to ask us as a separate use, are we worried about off-label use for another indication, whether it is in patients who receive chemotherapy or patients with totally unrelated disease states, that is a different question entirely.

This question, as I read it, is the CINV syndrome. And you have got to have the two together. And personally I think it affects the acute phase, and I think it affects the delayed phase.

CHAIRPERSON CAMILLERI: Dr. Brawley?

DR. BRAWLEY: Yes. I have a couple of questions for the company. They are very brief. As I look at the data, -- tell me if I am wrong -- when you look at the randomized trials of people taking

aprepitant, there is less use of breakthrough medications or salvaged anti-vomiting and anti-nausea medication in people who are on aprepitant versus not on aprepitant. Is that correct?

DR. HORGAN: That is correct.

DR. BRAWLEY: Okay. Now, of people who end up taking breakthrough medications, even though they are on aprepitant, is there evidence here that their quality of life is better, even though they are taking aprepitant and the breakthrough medications, when compared to individuals who are not taking the aprepitant?

CHAIRPERSON CAMILLERI: I guess I am going to allow you to show that quality of life slide after all.

(Laughter.)

DR. HORGAN: We didn't break it out. We looked at the global patient population. My colleague will show you that data assessing the impact of nausea and vomiting on patients' daily lives.

DR. BRAWLEY: Sorry.

CHAIRPERSON CAMILLERI: That's okay.

Thank you.

DR. MARTIN: Good afternoon. My name is Allison Martin. I am from the Epidemiology Department at Merck Research Laboratories.

Prior to showing the results of the quality of life data, I would like to give a little bit of background about the questionnaire so that you are fully informed about how we collected this data.

Slide 1602, please. So, as you know, the treatment goal for the aprepitant program was to prevent nausea and vomiting following chemotherapy. As a corollary goal, we wanted to assess the impact of nausea and vomiting on patients' daily lives and ideally eliminate any impact on their lives. And so we use the functional living index emesis questionnaire, which is a validated nausea and vomiting-specific measure to assess the impact of these symptoms on patients' daily lives.

The questionnaire contains 18 items, 9 of which refer to nausea, 9 of which refer to vomiting, which are 2 separate domains. The questionnaire was given to patients where they were asked to complete

the questionnaire on day six, and it had in cycle 1 with a five-day recall.

So basically it was asking the patients to rate the extent of the impact on the items shown on the bottom over the past five days. As you can see, it contains functioning items, such as enjoying meals daily, functioning household tasks, spending time with family and friends, et cetera.

The pre-specified endpoint, though, that was used for this questionnaire was a dichotomous endpoint. It was similar to the nausea visual analog scale. This is also the patients were making their ratings on a visual analog scale, which ranged from one, which is a great deal of impact, to seven, not at all or no impact.

The score, an average item score, greater than six was predefined as no impact on daily life because this is the uppermost bucket where patients were placing their marks anchored by not at all.

The next slide, please. This slide presents the results from the two Phase III protocols on the total score of proportion of patients in

protocols 052 and 054 reporting no impact on daily life. So, as you can see in both protocols 052 and 054, a significantly greater proportion of patients in the aprepitant-treated group reported no impact on daily life.

Can I have 1605? This is the same data, but, then, also included is a combined analysis of the two protocols, which was with nominal *p* values here, which, again, it shows the consistency of those data.

To head off Dr. Proschan's next question, can I please have slide 1606? This shows the cumulative distribution of these average slide scores based on the total score.

The way this works is the vertical axis is the percent of patients. The horizonal again is the scale that the patients were using to mark their responses. We have drawn in here the six cutoff that we used.

As you can see, over the full distribution, almost over the entire distribution, the aprepitant-treated patients had significantly greater scores. If you look at here, this is the 64 percent

on the total score in the control group who had a score of 6 or greater versus the aprepitant group, which had a score of 74 percent who had a score of 6 or greater. Again, on slide 1607 is protocol 054, which shows that these data are consistent.

The last thing that I will show is slide 1614, which, as Dr. Kevin alluded to in his presentation and what I had mentioned earlier that this questionnaire does contain two domains, a nausea domain and a vomiting domains, the analyses here show -- this is the results from protocol 052; 054; and, again, combined, and this was a post hoc analysis. These are nominal *p* values. But, as you can see, the data are consistent that we were superior to the control group in both the nausea domain and the vomiting domain across the two studies and in a combined analysis.

So overall I think these data are highly consistent with our clinical efficacy endpoints. And it shows that the aprepitant-treated patients had a benefit in terms of their ability to maintain their functioning in that five days following chemotherapy,

during a period when they would expect to have debilitating symptoms.

CHAIRPERSON CAMILLERI: Dr. Brawley, any supplementary question?

DR. BRAWLEY: No, sir. Thank you very much.

CHAIRPERSON CAMILLERI: Okay. Dr. Della'Zanna?

DR. DELLA'ZANNA: Okay. I don't want to complicate this whole discussion any more than we already have, but I do want to point out a couple of things in response to the firm's presentation.

As far as the impact on daily life in the overall phase, which was a predefined analysis, when the agency performed what they considered the appropriate multiplicity adjustment, including all predefined secondary and exploratory analysis, these *p* values were not significant. For study 054, it was 0.06. And for study 052, it was 0.25.

I don't want to distract from the focus of this question. I think we kind of are going in a little more detail than necessary to make our

decision. But I don't want necessarily to put all of our support on the data that was just presented.

CHAIRPERSON CAMILLERI: Dr. Michael Proschan?

DR. PROSCHAN: Yes. You know, one thing that one could do is say, "Okay. Everyone who took rescue medication would have had nausea if they hadn't taken it." That's one way of looking at it. And if you make that assumption, then effectively your endpoint is either nausea or rescue medication.

Now, that wasn't quite one of their secondary endpoints. I see everything except that on here. And I am wondering if that analysis was done and what the results of that were.

I mean, you could make various assumptions. You could assume everyone who goes on rescue medication would have had nausea or 80 percent of those would have had nausea. And if it's the case when you look at nausea or rescue medication, that is still significant, then that would be more evidence. I don't know if they have that.

CHAIRPERSON CAMILLERI: Have we got a

quick answer to that question?

DR. DELLA'ZANNA: I can interject on that a little bit and probably answer your response in a way you will like.

(Laughter.)

DR. DELLA'ZANNA: They did. With blinding, they analyzed and removed the "rescue therapy" that was inappropriately given as prophylaxis. So they pretty much did what you were just recommending. And the people who received or were counted as rescue therapy received it because they had established nausea.

So I know what you were saying as far as people who receive rescue medication, 20 percent were nauseous. Now, we can almost assume that the people who received rescue mediation, 100 percent were complaining of either nausea or vomiting.

DR. PROSCHAN: Right. What I am getting at is what percentage of those would have had a VAS score bigger than five because that is the real question. If 100 percent of them would have had a VAS score bigger than five, then essentially what it comes

down to is looking at the endpoint of either rescue medication or nausea.

And if that is highly significant or even lowly significant, that is some evidence.

DR. HORGAN: I think the best that we can do to address your concern is just show what the relationship was in the patients who did take rescue and what their visual analog scale scores were. We weren't able to because of the daily nausea ratings define the precise relationship, but we can show, slide 303 --

DR. PROSCHAN: I'm sorry, but you have all of these secondary endpoints. I was just wondering whether as a secondary endpoint, you looked at the endpoint of either bigger than five on the VAS score or rescue medication.

I mean, I see things that are very close to that under these secondary endpoints, but I don't quite see that one. There is a no emesis, no rescue, and maximum nausea less than five. But there isn't just no rescue and nausea less than five. So I was wondering if that were done.

CHAIRPERSON CAMILLERI: Would it be fair to assume that if people got rescue medication, their nausea score should have been greater than five?

DR. PROSCHAN: Well, my point is that if you make that assumption, then the relevant question is for the endpoint of greater than five or rescue medication, what are the results for that endpoint?

DR. HORGAN: One of our composite endpoints was total control. A patient in order to have total control was no emesis, no rescue, and maximum VAS score of less than five.

DR. PROSCHAN: Right.

DR. HORGAN: Would that address your --

DR. PROSCHAN: No. I mean, I see things that are tantalizingly close to what I want but not quite exactly.

DR. HORGAN: Right. The other thing that I think is probably the best thing that we can do to approximate your question is to look at the relationship between the nausea ratings and the patients who took rescue. To illustrate --

CHAIRPERSON CAMILLERI: Twenty seconds.

Okay. Then let's move on. I think we have discussed this point. When I heard the term "total control," I thought they were referring to Dr. Metz.

(Laughter.)

CHAIRPERSON CAMILLERI: Okay. I think we have discussed this sufficiently. We have clarified it. Let's get back to answer or at least respond to the question. We are kind of doing question 1B, has the aprepitant regimen been demonstrated to be effective in the prevention of nausea and vomiting in the delayed phase? Dr. Proschan?

DR. PROSCHAN: Yes.

DR. DESTA: Desta. Yes.

DR. McLEOD: McLeod. Yes.

DR. BRAWLEY: Brawley. Yes.

DR. KELSEN: Kelsen. Yes.

DR. LaMONT: LaMont. Yes.

DR. LEVINE: Levine. Yes.

DR. METZ: Metz. Yes.

CHAIRPERSON CAMILLERI: Camilleri. Yes.

DR. CRYER: Cryer. Yes.

DR. FOGEL: Fogel. Yes.

MS. COHEN: Cohen. Yes.

MS. HOFFMAN: Hoffman. Yes.

CHAIRPERSON CAMILLERI: Okay. Thank you very much. I think we can move on to the second question, is the designation of "highly emetogenic chemotherapy" appropriate given the regimens used in the clinical studies? I think what I would like to do here is ask our clinical oncologists to give us their opinion.

DR. KELSEN: I think it is. Cisplatin is a very difficult drug to take. Most of the patients, 80 percent, have 70 milligrams per meter^2 or higher. It is not fun to take 58 to 60 milligrams per meter^2. I think it is an emetogenic regimen.

DR. BRAWLEY: I would totally agree.

CHAIRPERSON CAMILLERI: Does the committee require any further discussion after the expert opinion? Dr. Fogel?

DR. FOGEL: I have a question. The wording here is "highly emetogenic." Can you explain clinically is there any difference between highly and moderate emetogenic? I mean, is this an issue that we

need to address in great detail?

DR. KELSEN: I don't think we need to address in great detail. This is a highly emetogenic regimen. I mean, in the days before antiemetics existed for platinum, it was very difficult.

I think by moderately emetogenic, they mean patients don't feel great, but they're not crippled as they would be when you take platinum without any coverage at all.

DR. BRAWLEY: In the doses that we frequently give, platinum before Reglan, very frequently people would become totally dysfunctional. Nowadays most people are able to function. Perhaps they can do even better with drugs like this.

So highly emetogenic in my mind means the person would be unable to function without drugs to treat the condition.

CHAIRPERSON CAMILLERI: Thanks, Dr. Brawley.

Dr. Cryer?

DR. CRYER: As I understand it, I think the reason that we are being asked this question is

that the previous standard to determine or define highly emetogenic was a previous cisplatin dose of greater than 100 milligrams per meter^2 based upon ondansetron approval.

So while I would like to get some clarification from Dr. Della'Zanna, when you removed the people who were on the lower doses of cisplatin, I guess that was less than 70. Did you say that it was maintained?

DR. DELLA'ZANNA: It maintained efficacy.

DR. CRYER: Efficacy?

DR. DELLA'ZANNA: Yes. And I should point out in the firm's behalf, which I'm sure they will state if I don't now, that the dose itself has varied in literature. If you look at the ondansetron oral formulation, greater than 50 was utilized and described as a highly emetogenic dose.

The one reason I brought this up is for two points, that this dose has evolved and that I just wanted to have clarification for future applications that this is now an acceptable dose that we can use as a label. And that's it.

CHAIRPERSON CAMILLERI: Thank you.

I believe that we are ready to take a vote on this. This time I am going to start with Ms. Hoffman.

MS. HOFFMAN: Hoffman. Yes.

MS. COHEN: Cohen. Yes.

DR. FOGEL: Fogel. Yes.

DR. CRYER: Cryer. Yes.

CHAIRPERSON CAMILLERI: Camilleri. Yes.

DR. METZ: Metz. Yes.

DR. LEVINE: Levine. Yes.

DR. LaMONT: LaMont. Yes.

DR. KELSEN: Kelsen. Yes.

DR. BRAWLEY: Brawley. Yes.

DR. McLEOD: McLeod. Yes.

DR. DESTA: Desta. Yes.

DR. PROSCHAN: Proschan. I have no idea. So I am going to abstain.

CHAIRPERSON CAMILLERI: Thank you. I think we can move on to the third question, can the recommended regimen be expanded beyond that used in the clinical studies to include the use of any 5-HT_3

antagonist as part of the aprepitant regimen?

We have to remind you that there were no studies with dolasetron. The studies that were presented in the documents pertain to granisetron and ondansetron.

The second part of the question, if not, what additional studies would you recommend?

Now, what I am going to ask, just to refresh our memories, Dr. Della'Zanna, can you remind us what other studies you had suggested might be appropriate, additional studies might be appropriate, as part of your presentation?

DR. DELLA'ZANNA: Presently we have intravenous studies on ondansetron and oral studies on granisetron. We do not have any oral information on ondansetron. Now, agreeing with our PK information, it is metabolized for multiple pathways.

So the likelihood of a PK interaction is not that high. But the other interactions we can't predict. As far as dolasetron, we have no safety data whatsoever.

CHAIRPERSON CAMILLERI: Okay. This is

where we need our clinical pharmacology colleagues also to help us out. Would you like to make any statements or clarifications?

DR. McLEOD: I believe Dr. Desta pointed out that the way that dolasetron is activated and then metabolized does mean that a fairly large fraction of the population is going to be relying on CYP3A4 for the inactivation of the drug.

So that while carbonyl reductase is involved, it's reactivating it. There are two enzymes, the CYP2D6 and 3A4, that are then inactivating that metabolite, that active moiety.

As Dr. Desta mentioned, ten percent or so of the general population are defective in that pathway. And so they basically are 3A4-dependent. So it does raise the question of whether there is a viable interaction at that point.

Without any data, it is hard to decide whether it is relevant or not. It could have zero relevance or it could be dramatically important.

I also would like some clarification from probably Dr. Della'Zanna on the robustness or whatever

you can call it of the QT prolongation concerned with dolasetron to see whether this is a true problem or one that is just a concern. If in practice this 5-HT_3 antagonist behaves as the other two, then I think we are just talking about theory and not reality.

CHAIRPERSON CAMILLERI: Dr. Della'Zanna, have you got a response on QTc prolongation with dolasetron?

DR. DELLA'ZANNA: I do not have access to that information now to present.

CHAIRPERSON CAMILLERI: Dr. Desta?

DR. DESTA: I think with ondansetron, oral drug interaction, I don't think there will be a big difference -- that is my opinion -- with ondansetron oral because we didn't see it or they didn't see it with the other drug, which is exclusively a substrate drug. So I don't think that will really matter unless otherwise this drug inhibits 2B6 in a significant way because 2B6 is involved with also ondansetron.

The other one I agree with Howard is how concerned are you or is there any dose-response relationship of dolasetron and QT interval

prolongation? For example, in poor metabolizers, are there any documented things or is there any drug interaction that really concerns you?

Otherwise if you take that drug, the metabolic pathway, which is shared by 3A, is small. So if you block that, could we get higher plasma concentration whereby we can have some QT interval concerns?

CHAIRPERSON CAMILLERI: So if I am understanding you correctly, Dr. Desta -- and excuse me. I am not a pharmacologist. Your first statement was that, even though there haven't been studies with oral ondansetron, you as a pharmacologist, you are quite reassured by the data that you see pertaining to the pharmacokinetics of granisetron, another 5-HT_3 antagonist that shares the same metabolic pathway as ondansetron. That was the first point. Is that correct?

DR. DESTA: Yes, correct.

CHAIRPERSON CAMILLERI: Okay. Second point pertained to the question as to, again reflecting Dr. McLeod's question, how much of a risk

is there with the dolasetron relative to QTc prolongation? I am assuming that somebody from the company has something they really want to say.

DR. GRUNDBERG: I am Steve Grundberg. I am a medical oncologist from the University of Vermont here as a consultant to the company. We have done a lot of the developmental work on these various antiemetics.

The QTc question has been around for a long time. I would have to say we are partly responsible for it because when we did the Phase I's on dolasetron, it went to extraordinarily high doses and we were able to see a QT change.

It is not just the effect of dolasetron. That is a common misconception. It has also been described for ondansetron by both Gralla in New York and by Benedict in Texas. There has really not been any clinical significance to it. I don't know any oncologist who would not use any one of these three drugs for that reason.

CHAIRPERSON CAMILLERI: Dr. Kelsen, is that in agreement?

DR. KELSEN: I can't comment on the QTc interval. That is not my area of expertise. But the drugs are widely used interchangeably.

I guess the question here is if you're precedent-setting and you are looking a little bit down the line, if you didn't actually study the drug with the other drug, what do you do?

CHAIRPERSON CAMILLERI: I think that really encapsulates our dilemma.

DR. BRAWLEY: Pardon me. I never knew dolasetron existed until I started reading this stuff. Granisetron and ondansetron are very commonly used in my experience, but dolasetron I don't think is a wide market share.

CHAIRPERSON CAMILLERI: Go ahead, Dr. Metz.

DR. METZ: It seems to me that from the agency's point of view, people are concerned that unless you actually have tested a specific agent, it is going to be a problem to make a statement going forward.

But, on the other hand, I think from the

company's point of view, you have to sort of say that we are going to look at representative examples of each class because you cannot expect that you are going to do a study on every single member of every single class.

I was just very reassured by the most recent comment that these drugs are really used interchangeably and that the QTc issue doesn't really pertain only to this one particular agent.

CHAIRPERSON CAMILLERI: In addition to that, I am assuming that you are quite reassured that dolasetron is not primarily metabolized by the 3A4 pathway.

DR. McLEOD: Well, in 90 percent of the people out there, there are two enzymes degrading the drug. So you knock out 3A4 and you've got 2D6 to pick up the slack. In ten percent of the population, at least in theory, you would predict they would be very reliant on 3A4.

It's the consequence of that that is unclear to me. If you alter the 3A4 metabolism of the active metabolite of dolasetron, is that a big issue?

I don't know the answer to that.

CHAIRPERSON CAMILLERI: Very brief comment.

DR. PETTY: A very brief comment regarding dolasetron. Dolasetron** is cleared primarily by CYP2D6. Although it is not in the label, there is reference in documents available by Freedom of Information to indicate that poor metabolizers of CYP2D6 had a roughly two-fold increase in their AUC of hydrodolasetron and in patients who received verapamil and diltiazem, which would have comparable 3A4 inhibition to aprepitant. There was no effect on hydrodolasetron clearance.

CHAIRPERSON CAMILLERI: So do you want to interpret that for clinical gastroenterologists?

(Laughter.)

DR. McLEOD: Since we're on record, I will give a formal interpretation. It looks like if you take patients who are deficient in 2D6 based on what was just stated, if you have the two enzymes that degrade the drug, the active metabolite, if you take patients who have one of them knocked out because of

genetic abnormalities and you then inhibit or alter in any way, inhibit or induce on the examples he gave, the 3A4 component, the remaining component, there were not dramatic changes in either the pharmacokinetics or the toxicity profile. So the statement that was made suggests that in those people that we were worrying about, it is not going to be an issue.

CHAIRPERSON CAMILLERI: Thanks for that clarification. Dr. Fogel?

DR. FOGEL: I just want to make a comment about QTc intervals in studies since we are going to be precedent-setting. One of the things we learned from cisapride is that if you have electrolyte abnormalities or concurrent illnesses or comorbid conditions, your risk of having fatal arrhythmias tends to be increased.

Since we are going to be dealing with patients who are off studies, not protocols, who are going to be very sick, who get these regimens, I think we need to be databased in any decisions that we make.

CHAIRPERSON CAMILLERI: Thanks for the comment. Other discussion on this point or

clarifications requested?

(No response.)

CHAIRPERSON CAMILLERI: If not, I think we should move ahead to try to answer the first part of this question, can the recommended regimen be expanded beyond that used in the clinical studies to include the use of any 5-HT_3 antagonist as part of the aprepitant regimen? Dr. Proschan?

DR. PROSCHAN: This is another --

DR. McLEOD: Let's start on that side.

DR. PROSCHAN: This is another one where I think I have to abstain because I think it takes clinical judgment. And I have at most statistical judgment.

CHAIRPERSON CAMILLERI: Dr. Desta?

DR. DESTA: Desta. Yes.

DR. McLEOD: McLeod. Yes.

DR. BRAWLEY: Yes with a request for post-marketing studies.

CHAIRPERSON CAMILLERI: That was Dr. Brawley.

DR. KELSEN: Kelsen. Yes.

DR. LaMONT: LaMont. Yes.

DR. LEVINE: Levine. Yes.

DR. METZ: Metz. Yes.

CHAIRPERSON CAMILLERI: Camilleri. Yes with a request for further studies.

DR. CRYER: Cryer. Yes.

DR. FOGEL: Fogel. No. You have at least one 5-HT_3 receptor that has been approved that has been shown to be safe and effective. I think unless you have additional data, you should not generalize. Even though other combinations may very well be safe, you just don't have the data at this time.

MS. COHEN: Cohen. No. I think this is precedent-setting. If there is another study, we shouldn't be making these decisions. And there are consequences, and there is not any data. This rush to publish is very frightening to me.

MS. HOFFMAN: I'm tossing back and forth here. I am going to go with no with further dolasetron studies recommended.

CHAIRPERSON CAMILLERI: Thank you.

Have we recorded that for the record?

Thank you.

The second part of that question was, what additional studies would you recommend? Was it, Dr. Brawley, you recommended some additional studies?

DR. BRAWLEY: Yes. I would like to see some pharmacologic studies with dolasetron and EMEND. very much as we saw with ondansetron and granisetron.

CHAIRPERSON CAMILLERI: I am assuming that you are happy with the oral ondansetron story.

DR. BRAWLEY: Yes, I am happy with the oral ondansetron study. Actually, Dr. McLeod's conversation a little earlier made me much more comfortable with approval of a dolasetron and EMEND combination.

CHAIRPERSON CAMILLERI: Yes. I was also requesting further studies with dolasetron. My overall reason to say yes was that I was quite **persuaded by the information that the metabolism of dolasetron was unlikely to be very dramatically altered in this context. But I think further studies would be very useful.

Other comments?

(No response.)

CHAIRPERSON CAMILLERI: Okay. Can we move on to question number 4? This is a long one. Aprepitant is an inhibitor of the CYP3A4 metabolic pathway. For chemotherapeutic drugs that are metabolized by this pathway, moderate inhibition of their metabolism could result in serious or life-threatening toxicity.

So the first thing we are going to do is we are going to address the issue pertaining to 4A. The applicant has analyzed the safety data by chemotherapy regimen. And a significant number of patients received etoposide, vinorelbine, or paclitaxel, all of which are substrates for CYP3A4, in combination with cisplatin and the aprepitant regimen.

Here are the questions. Is this data sufficient to support the safety of aprepitant in combination with these specific drugs; that is, etoposide, vinorelbine, and paclitaxel?

Would anybody like any questions answered or can we go ahead and address and answer the question?

(No response.)

CHAIRPERSON CAMILLERI: I see no lights coming on. So I think this will probably be the easier part of the question. So we want to know is there sufficient data to support the safety of aprepitant in combination with the drugs etoposide, vinorelbine, and paclitaxel? This time we will start with Ms. Hoffman.

MS. HOFFMAN: There was a comment about sepsis being three times as high with the vinorelbine. Can you just discuss that briefly again?

CHAIRPERSON CAMILLERI: Dr. Proschan, I believe you sort of addressed that question slightly by saying there are multiple comparisons being done here and you felt that the signal here was relatively small considering the very small number of instances.

DR. PROSCHAN: Right. And that's why I think it is impossible from this data to say, "Okay. It is harmful." Likewise, I think it is impossible to rule out harm.

So to me, there hasn't been sufficient data to establish safety, but it might be very hard to

have sufficient data to establish to a high degree of certainty that it is safe.

CHAIRPERSON CAMILLERI: Dr. Della'Zanna, do you have any other comments?

DR. DELLA'ZANNA: That was exactly what I was trying to get across. I wasn't trying to say that this should not be used in conjunction with vinorelbine. I was trying to suggest that this might represent a small signal that we could not define. One of my concerns was some of these respiratory serious adverse events as well as the incidence of infections.

Like I said, -- and I will emphasize it again -- the numbers are very small. However, the numbers that were serious infection-related adverse events were only seen in the aprepitant group. So that was what I was trying to focus on.

And from that, I wasn't necessarily looking for condemning the use with vinorelbine, just the committee's opinion on whether additional information is necessary.

DR. PROSCHAN: Wasn't it also the case

that several of those events were at the same site, same --

DR. DELLA'ZANNA: The significance of that is uncertain for me only because this one site focused predominantly on lung cancers. So the fact that these all occurred in one site does not surprise me that this site focused and is concentrated in lung cancer.

The firm stated that it was balanced between the two treatment groups at the number of patients with these primary lung cancers. It wasn't biased.

CHAIRPERSON CAMILLERI: Dr. Kelsen?

DR. KELSEN: I think we have all indicated that it works to decrease nausea and vomiting. So it is effective in that setting. I have a question for the agency because I think this is where -- you know, I am just a visitor to this. But as an oncologist, is there a precedent for using an agent like this in which one feels pressed into indicating exactly which drugs it can be given with, as opposed to it's recommended for highly emetogenic chemotherapy, as represented by cisplatin, because we are now facing a

situation where you are going to try to tailor the specific combination regimens, not only class by class but almost drug by drug, on the basis of not much data?

Has this ever come up to you all before? Is there anything to guide us?

DR. HOUN: Well, it frequently comes up because when drugs are tested and to be used with other drugs, what are these other drugs? How do you label? And so the reason why we are airing this is because we want the public to know that we have discussed this.

So when the agency gets criticized that you didn't look carefully that they only had enough patients in these three drugs, why are you giving it broad labeling for everything, we want to say, "Well, you know, we are aware of those issues. And we brought it to the public's attention. We have had a discussion about it."

So that is why it is here. It is not our desire necessarily to state specifically which of these drugs, but those were the ones that had a lot of

patients. And there will be other drugs that didn't. How do you guys help us with advice on handling that?

DR. KELSEN: I would like to make just one other point, that these are all intravenous drugs. I was struck by the comment that it may be oral agents that become an issue. We are working very, very hard to switch to oral chemotherapy. There are a number of models of that. I don't think this is a trivial issue at all.

DR. DELLA'ZANNA: The other think I would like to bring up -- and I realize that the inhibitory effect is greatest on the oral. We seem to play down the fact that the IV methylprednisolone had a 35 percent increase.

The tables that were demonstrated on the slides were somewhat misleading, as far as I'm concerned, when you considered the dexamethasone dose and the divergence of the two lines were generous. Then when they showed the methylprednisolone IV, you can almost superimpose them, even though there was a 35 percent difference.

And if you want to pull up your slide that

I am talking about, I have it here. Where is it? We can just keep going forward, though.

CHAIRPERSON CAMILLERI: Ms. Hoffman, do you have another question? Yes, Dr. Levine?

DR. LEVINE: Just we shouldn't jump ahead to the next sentence, but I would like to know whether pre-approval or post-approval, what kind of time frame would it be to get satisfactory numbers and data for either pre or post-approval regarding the issue we are talking about from the agency?

DR. JUSTICE: I think we discussed the wording of this question to some extent. I think in terms of pre-approval, we are talking we could deal with that in labeling if we thought there was a potential drug-drug interaction that was significant enough that the drug should not be used in combination with another drug. We could address that in labeling and until a study was done to document that there is or is not a drug interaction.

So I don't think we are asking whether an actual study would have to be done pre-approval. So our question is a little bit misleading.

DR. LEVINE: Thank you,

CHAIRPERSON CAMILLERI: Maybe I could ask Dr. Della'Zanna whether there would be any advantage in splitting up this trial of drugs. It seems to me that you had very little concern about the combination with etoposide and paclitaxel. And, yet, from the response to Ms. Hoffman's question, there still are some reservations with regard to vinorelbine in combination.

DR. DELLA'ZANNA: The most significant thing that I noticed on the vinorelbine was the pulmonary insufficiency that was ultimately fatal and then that you included an additional two fatalities that were serious infection-related. And then in the corresponding standard therapy group, there were only two fatalities, neither of which were related to truly a pulmonary problem other than a pulmonary emboli and a death that was reported as unknown.

CHAIRPERSON CAMILLERI: But I remember that we got some information that the vinorelbine toxicity appeared not to be related to the usual bronchospasm and acute syndrome but appeared more

related to the underlying lung disease.

Thirty seconds.

DR. REINES: Okay. If I could have slide 755, please? I really want to echo the comment that when we pull things apart in different ways, the results aren't always balanced. We pre-specified the AEs, as I told you in my main talk, that were indicative of chemotherapy-induced toxicity.

These are the data for vinorelbine. The pre-specified AE incidences were the same for both groups. The infections were higher, as we have been discussing, in this group.

If you look at hematological AEs, it goes in the other direction, which you haven't been shown yet. But that is how the numbers come out overall the same.

So we have looked very carefully at this. We did think that the respiratory issue was not a vinorelbine type of toxicity. And we looked very carefully at the hematological toxicity with this drug. There is no evidence that aprepitant is enhancing that toxicity.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Levine?

DR. LEVINE: Just in reference to another large study that is just developing post-marking on an approved drug, was there any evidence on pulmonary function tests that were done in these patients, either before or after death? And was there a diffusion defect or pulmonary hypertension that developed in these patients due to drug?

DR. REINES: No.

DR. LEVINE: It was done or not done, pulmonary function tests?

DR. REINES: We don't have that information. It was not done as far as I know.

DR. BRAWLEY: Quick question for a statistician. Are we technically doing the subset analysis here? And substantive analysis is inherently flawed and likely to give you the wrong answer.

DR. PROSCHAN: Right. I mean, that's why I said earlier if you try and attach a statistical significance to this, it is going to be very difficult because you are looking at so many different drugs, so

many different outcomes.

We have been focusing on the ones in which you see some trend. But even in the ones in which there is no trend, where it looks dead even, there still could be harm that you just can't see with this number of patients.

So if you really want to prove that there is no interaction with any of these drugs, it is going to take thousands of patients to do that.

DR. BRAWLEY: That brings us back to Dr. Della'Zanna's original comment, which is that we should be cautious because these are all small numbers and small trends that may mean nothing, may mean something.

CHAIRPERSON CAMILLERI: Okay. I believe we have had sufficient discussion. Any other clarifications needed on this specific point?

(No response.)

CHAIRPERSON CAMILLERI: Dr. Proschan, I am going to start asking you to vote this time again. The question, therefore, is, are the data sufficient to support the safety of aprepitant in combination

with the drugs etoposide, vinorelbine, and paclitaxel?

DR. PROSCHAN: I don't think they are, but I think it would take thousands to make it so.

CHAIRPERSON CAMILLERI: I am assuming that Dr. Proschan's answer is no.

DR. PROSCHAN: As stated, to this question as stated, I would have to say no.

CHAIRPERSON CAMILLERI: Dr. Desta?

DR. DESTA: I'm not sure.

CHAIRPERSON CAMILLERI: This is the time to come off the fence, Dr. Desta.

(Laughter.)

CHAIRPERSON CAMILLERI: You could abstain. Sorry. I thank you.

DR. DESTA: Because the question is "Is this data sufficient to support?" it is "Yes" or "No." And we don't know. I don't know.

CHAIRPERSON CAMILLERI: I am assuming that is an abstention, then. Dr. McLeod?

DR. McLEOD: McLeod. Taking all three drugs together, which is the way the question is posed, I would say yes.

DR. BRAWLEY: Brawley. I'm very much on that fence, but I'm leaning over into the yes. So I'll go yes.

DR. KELSEN: I'll say yes. And they will need those additional studies.

CHAIRPERSON CAMILLERI: That was Dr. Kelsen.

DR. LaMONT: No. The data is insufficient. LaMont.

DR. LEVINE: I'm uncomfortable with it, but I will say yes. From these other experiences with post-marketing, as all of you are saying, these are very serious consequences. Therefore, I am looking forward to the next sentence, but I would say yes.

CHAIRPERSON CAMILLERI: That was Dr. Levine. Now Dr. Metz.

DR. METZ: I'm going to say yes within the limitations that this is designed in such a way that you actually cannot answer the question because there are not enough patients. But what I would like to see is post-marketing data. I think that is very important. I don't want the fact that this may

ultimately be an issue to limit the availability of this agent. So that is why I am voting yes.

CHAIRPERSON CAMILLERI: Camilleri. Yes with additional studies post-marketing.

DR. CRYER: Cryer. Yes with additional studies as well.

DR. FOGEL: Fogel. Yes with additional post-marketing studies.

MS. COHEN: Cohen. No because can you tailor a regimen? What kind of advertising is there going to be? Was this oral versus the IV? There is just not enough data.

Post-marketing, what happens to us who get caught before the post-marketing if it's used? I think it is too chancy.

MS. HOFFMAN: Hoffman. Yes with post-marketing studies.

CHAIRPERSON CAMILLERI: Thank you.

So I think we have kind of answered what additional studies are going to be needed. Do we need to address it any further? Does the agency want us to specify what sort of post-marketing or other studies?

DR. HOUN: I think if people do want to give suggestions on endpoints, that would be helpful.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Metz?

DR. METZ: If I may comment, it is not so much what the endpoint is and it is not so much on what the design of the study is going to be. What I think is important is you have to realize that any drug that is ever going to be marketed for a specific indication ultimately is only going to be studied in so many patients. We will have to learn as time goes on.

They will certainly be patients who get this drug or any other drug at any time with a life-threatening cancer illness who may get sick. And the signals are hard to find. You people are the experts on post-marketing surveillance problems and also on the fact that there's no really good way to fix it, which brings us back to all the other previous discussions we have had in this committee.

I think it is important to just realize that this is a possibility and that patients will get

as good care as they can from the individual doctors and that as data accumulates, information will be acquired.

CHAIRPERSON CAMILLERI: Yes. Dr. Kelsen?

DR. KELSEN: I am going to make a suggestion sort of to us at ODAC. One way to address the survival issue, which we were not able to address, is to recommend that when future studies are done in lung cancer, that they specific the antiemetic regimen very rigidly so that all patients not only get the same chemotherapeutic regime, they get the same EMEND or whatever this is regimen. And then you will have an answer as to whether there is an effect on survival.

We will not be able to address safety because I think both arms will get the same thing. But you will know what the survival outcome is.

CHAIRPERSON CAMILLERI: Dr. LaMont?

DR. LaMONT: Yes. I wonder if we could learn anything from the times of exclusions that were used in the clinical studies because, as someone has already mentioned, this is going to be opened up to

all kinds of cancer patients with all kinds of backgrounds.

So I assume that the patients who had had previous infection or recent infection or fever, et cetera, et cetera, leukopenia, neutropenia were excluded. Perhaps we can build some of those safeguards into the indications and post-marketing surveillance.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Horgan?

DR. HORGAN: The enrollment criteria were quite broad. And we obviously wanted to exclude anybody with an active serious infection. We had exclusions for low neutrophil counts and abnormal white cell counts and renal function and liver function that would be consistent with what the normal criteria for the administration of chemotherapy were.

In general, we excluded patients who are receiving potent inhibitors of CYP3A4 and inducers of CYP3A4, but apart from that, the exclusion criteria were very similar to what have been used in previous antiemetic trials to allow a population that was as

representative as possible to clinical practice to be studied.

CHAIRPERSON CAMILLERI: Dr. McLeod?

DR. McLEOD: I think as we get into Part B of this question, it will come out even further. But as far as suggested studies, most of the concerns that have been raised so far have been of a pharmacokinetic nature.

Now, whether it starts with pharmacodynamic variability is to be seen, but certainly there could be some very defined minimum studies where the presence of a pharmacokinetic interaction is evaluated.

These studies do not have to be done fairly quickly, but if there is no pharmacokinetic interaction clear from even single-dose combination studies with this agent and the chemotherapy drug, that will give us some further confidence on its use.

It would not be enough to declare that it is safe for all mankind, but in the context of Dr. Metz's comments, we are not robots. This is not computer circuitry and engineering. There are some

studies that have to be done and learning that has to go on that is beyond the scope of the FDA.

CHAIRPERSON CAMILLERI: Dr. Kelsen?

DR. KELSEN: Just one last comment to follow that up. You could imagine a study where women with breast cancer commonly receive single-agent vinorelbine. It's not very emetogenic, but you could easily do a small trial with this agent. And with single-agent vinorelbine, you would get your answer in 15-20 women.

CHAIRPERSON CAMILLERI: I'm assuming somebody would want to know about pulmonary function, transfer factors, and all the other things related to vinorelbine, peak flow rates, capacity, et cetera, to at least start to address that question in the context of the pharmacokinetic study as well.

I believe we can move on to question 4B, few or no patients received docetaxel, vinblastine, vincristine, ifosfamide, irinotecan, or imatinib, which are all substrates for CYP3A4, in combination with the cisplatin and the aprepitant regimen. The docetaxel drug-drug interaction study has accrued only

five patients. We have seen the data.

So the question is, is there sufficient data to support the safety of aprepitant in combination with these drugs? Does anybody want further discussion before we take a vote on this? Dr. Metz?

DR. METZ: Yes. I'm sorry to harp on the same point today. I don't know actually if there is any real difference if you say five people have had docetaxel, nobody has had vinblastine, and a whole number but not enough have had vinorelbine.

So I think it is the same question. I think you are really asking us the same question. In the subgroup that wasn't big enough, well, here is a subgroup that is even smaller. It is going to be the same kind of response that I would have to make.

So no. But the only way we are going to find out is by testing enough patients.

CHAIRPERSON CAMILLERI: We have a quick, enlightening question. Dr. Levine can tell us in the meantime this question.

DR. LEVINE: It would just seem to me from

the former answer that we had on pharmacokinetics I would feel reassured with a pharmacokinetic study for all of these pre-approval.

CHAIRPERSON CAMILLERI: Let's have some further insights. Good.

DR. ROWLAND: Yes. I was reflecting on the question that I was asked this morning.

CHAIRPERSON CAMILLERI: Can you introduce yourself, sir?

DR. ROWLAND: I was reflecting on the answer that --

CHAIRPERSON CAMILLERI: Who are you?

DR. ROWLAND: Sorry. My name is Malcolm Rowland.

I was asked the question before about the docetaxel study. And I was reflecting on it over lunch and asked the company if they would have data available to bring up a number of points. If I could have slide 1113? Can I have that? Because I think there are several things that are going around. And I think we may not have as clear a picture.

The point I was making before was that, in

fact, in answer to the docetaxel issue is that this is an intravenously administered drug. The interaction we are looking at is whether intravenously drugs are affected.

There are three or four substrates that are affected. This is the group of drugs over here that we are talking about that was actually done. So we have already talked about methylprednisolone, ondansetron, erythromycin, and docetaxel. Docetaxel, it is inferred that that may not be representative.

I am a little worried about that because the FDA has and many people have advocated the use of enzymology and an understanding of that enzymology in order to make some statements about how we think some things are happening so that we don't have to study every drug X that comes along but we use sound scientific principles.

Docetaxel, to my knowledge, has been one which has been correlated with what is known as ear, throat, mouth and breath test, which is used as a test for the systemic activity of 3A4 and has been correlated with midazolam. So to say that this is not

representative of 3A4 doesn't make sense to me. You may want to think about that.

I think the other thing is, as I said, there is very little effect on intravenously administered 3A4 substrates. Where we see the effect more -- and I think it was pointed out that they are moderate -- is to drugs where the drugs are given orally. And that is because it occurs in the *response of the drug at the interstinal level. And so we see it there. These were the magnitudes that were discussed this morning. So I want to indicate to you that the route of administration is very important.

Another thing that was suggested was this issue of polymorphism. To my knowledge, there is no polymorphism in CYP3A4. It is a unimodal dispersion in the population. We know very little about what correlates with that variability. I know of no diagnostic that would predict the CYP3A4 activity other than giving the drug and looking at what is going to happen. So we don't have polymorphism, but we do have variability.

So if I can relate this back to a slide which was done, 36, if I can have that, which was the thing that was striking me, -- this is 36 -- and we are talking about this drug being in this thing, which is moderate, the same or very similar to grapefruit juice, verapamil, and diltiazem, then it seems to me that if there is a question of concern about this drug, then presumably there is a question of concern about these other drugs, too, because, as far as I can see, I can't tell the difference. If you just gave me the data and didn't tell me the drug, I wouldn't know the difference. So those are my comments.

CHAIRPERSON CAMILLERI: Thank you. I guess the other drugs and grapefruit juice are not up for discussion today.

DR. ROWLAND: All right. I appreciate that.

CHAIRPERSON CAMILLERI: Dr. Della'Zanna?

DR. DELLA'ZANNA: I have two points I want to bring up. Okay? First of all, the other drugs that you were talking about do not have the same narrow therapeutic index. The effect that we saw with

IV methylprednisolone was a 35 percent increase in area under the curve. Okay?

Now, that still might be labeled for you as a small increase, but if you increase the plasma levels of some of these cytotoxic agents by 35 percent, you might be breaching into a toxic level.

DR. ROWLAND: Can I just respond? I mean, I think there are two aspects. One is the magnitude of change that occurs when you bring drugs together. And the other one is the therapeutic implication of a degree of change.

I think one thing that is very clear about 3A4, it's highly variable. If I give a drug, a standard dose, to anyone, I have no knowledge of what that variability is going to be. So people who are getting standard doses are getting a four to five-fold variability and exposure full stop, before we even start.

And we live somehow. Somebody lives with that. I mean, presumably it's clinical management. Maybe one day we will have diagnostics associated with that.

DR. HOUN: You expressed our responsibility in terms of FDA's public health responsibility and the difficulty of it very well.

DR. ROWLAND: I appreciate that. We are all looking for the diagnostic, the prognostic that would predict the handling in individuals.

CHAIRPERSON CAMILLERI: Thank you for your intervention.

Yes, Dr. Cryer?

DR. CRYER: I just wanted to follow up on a comment that you were making, Dr. Della'Zanna, with respect to the corticosteroid-related increases in serum concentration. So in the clinical studies that were done, as I understand it, the dexamethasone dose on subsequent days was reduced to provide plasma concentrations that were similar to control.

So the question, the specific question, I have in that regard is, is it proposed for the label that the dexamethasone dose would similarly be reduced in subsequent days' doses with the aprepitant-antiemetic combination?

DR. DELLA'ZANNA: Yes. The dexamethasone

dose was decreased not only for subsequent days but also on day one. My concern is we saw that interaction, resulted in decreasing the regimen by 50 percent, but we haven't applied or even really analyzed whether that same interaction is going to occur with cytotoxic agents.

There are no recommendations mentioned in the label saying that if you're on vinorelbine, decrease your dose by 50 percent. It's not there because we don't know. It hasn't been evaluated. That is my concern for this.

If we saw these kind of effects in dexamethasone and the effect was enough to decrease and change the regimen but we haven't looked in the cytotoxic agents, realizing that yes, the inhibitory effect is much more on oral drugs, we can't ignore the fact that the IV methylprednisolone resulted in a 35 percent increase.

DR. CRYER: You raised an important point that I actually had forgotten. That was a point that struck me earlier, which was that the effect of aprepitant on the potential to raise plasma levels of

chemotherapeutic agents was, as you rightly pointed out, has only been done with aprepitant alone, rather than the combined antiemetic combination, which will actually be suggested for use in clinical practice.

And so that would definitely be an area for studies that would need to be looked at. And that would be the effect, I think, with the combined antiemetic therapy, for which we have no data on at all, as I understand it.

DR. ERB: But we have clinical data on it.

DR. REINES: Yes. The point that we wanted to make was that that is what our clinical safety data reflect. That is what we are asking you to consider. All of those clinical data, of course, in Phase III were with the regimen, not with aprepitant alone. And so our safety argument is the argument for the regimen.

CHAIRPERSON CAMILLERI: Dr. Fogel?

DR. FOGEL: I have a question for the agency. Given the dynamic nature of chemotherapy and given, as has already been alluded to, we are going to be moving from intravenous to oral medications,

hopefully there will be lots of new and more effective medications coming to market in the course of the next few years, what is the agency's thoughts about sort of how drugs are approved?

Is the agency believing that to avoid criticism, these approvals should be very narrow so that you can only use certain combinations or does the agency believe that there should be a certain amount of openness in the approvals with extensive post-marketing data collection?

DR. HOUN: I think that's a difficult question. I think it will depend on the specific drug alternatives, the indication. And if you have a new drug for a life-threatening indication, no alternatives, what amount of safety data you have may be less than if you had a me, too, fifth-of-a-kind that you are trying to bring to the market as a new molecular entity.

I am thinking that because these are difficult questions and because the public should not, as our consumer representative, patient representative said, be blind-sided, that this is a public

discussion, it's for the record, it's on the internet, that issues be publicly vetted so that we can hear what the experts are saying, there is a chance for the company to respond as well as public input because these are difficult questions. These are policy questions. There is not a right or wrong. It's judgment.

DR. FOGEL: The reality is that you are probably going to be second-guessed, no matter what happens. If this is a safe drug, you are going to be criticized for not having a broad use. And if it turns out that, unfortunately, somebody has a serious adverse side effect that kills them, you are going to be criticized for being too liberal. You can't make a decision based on the data that we have.

We are all stuck by this. And I think that by having these discussions and sort of having the label written with this ambivalence put in where it's clear that the data is not available for a broader use would be very helpful. And I think it would help direct physicians.

CHAIRPERSON CAMILLERI: Thank you, Dr.

Fogel.

Other questions or clarifications required on this point?

(No response.)

CHAIRPERSON CAMILLERI: If not, I want to remind you of the question that we are asked to try to answer. The question is very specific, is there sufficient data to support the safety of aprepitant in combination with the drugs docetaxel, vinblastine, vincristine, ifosfamide, irinotecan, imatinib? Dr. Proschan?

DR. PROSCHAN: I think the answer is no as written here.

DR. DESTA: No as written here.

CHAIRPERSON CAMILLERI: That was Dr. Desta.

DR. McLEOD: McLeod. No with specific post-approval or pre-approval if deemed necessary studies.

DR. BRAWLEY: Brawley. No.

DR. KELSEN: Kelsen. No.

DR. LaMONT: LaMont. No.

DR. LEVINE: Levine. No.

DR. METZ: Metz. No with a request for post-marketing studies and specific concerns relating to future oral chemotherapeutics.

CHAIRPERSON CAMILLERI: Camilleri. No.

DR. CRYER: Cryer. No.

DR. FOGEL: Fogel. No. And I think that small studies actually aren't going to help you very much. It is only when there is widespread use of a drug that you are actually going to get the answers that you need.

MS. COHEN: No. And I hope I don't have to give an answer to it.

MS. HOFFMAN: Hoffman. No.

CHAIRPERSON CAMILLERI: Thank you.

Do you require any further clarification on the types that would be useful to address 4B?

DR. HOUN: Yes. I think we should have some discussion. Everybody voted no. There has been a proposal that this be handled strongly in labeling so that this ambivalence on we don't have information be placed in the label.

My interpretation means that you are interested in studies post-marketing. I just want to confirm that. Are there people who are saying some of these studies should hold up the approval for the drug?

CHAIRPERSON CAMILLERI: Ms. Cohen seems to have an answer.

MS. COHEN: Well, as you can gather by now, I spent part of my life in consumer protection. And part of my expertise is in advertising. I see advertising for pharmaceuticals that FDC and FDA is finally recognizing is deceptive. I am looking at one of the proposals for a package insert. If that is plain language, then it is certainly not English that I understand.

I am concerned that you don't have enough studies. People are not getting the care that they need nowadays. Doctors don't have time to speak to them. They become a little cavalier.

And I don't think people should have to say post-marketing, "If someone dies, then we have learned something." Why can't we learn something

before they die? I think it is very cavalier.

The practice of medicine today has changed dramatically. I am boring some of you. I am looking at your faces. But when it hits a member of your family, then you care. And I am here to see that consumers get the attention they need and they are not getting anymore.

There is just not enough evidence. When I hear about sepsis and toxicity, oral versus IV, there are so many adverse events. Just making notes, drug-drug reaction, drug reaction to the drug, I am sitting here. Is this safe and effective? What are we here for? It is not the bottom line.

I own Merck stock. But, believe me, I would rather take less money for it and know that my consumers are going to be protected. This is a tough world, and we have to help people.

I am sorry if I am giving you this speech, but you can see I am upset. I am worried. What is the next generation going to do?

CHAIRPERSON CAMILLERI: Thank you.

Can I ask Dr. McLeod to specify what

pre-approval studies he would recommend? Did I understand you correctly?

DR. McLEOD: Well, I didn't know whether to define whether it needs to be pre-approval or not because I haven't had time to think through the implications of that.

One thing I was just doing right now because of Ms. Cohen's comments was looking through the drugs that were commonly co-administered with this agent as a place to start because, I mean, all anti-cancer drugs are possibilities to be combined with cisplatin and this antiemetic regimen, but there are certain players that are going to be very common, such as the ones there.

So, for example, the docetaxel study that is ongoing now is recognized by everyone, including the applicant, that that is an issue, that cisplatin, docetaxel is going to be a common combination in which this drug will be added. So they are already on their way with that study. And that needs to be expedited. I think that needs to be done pre-approval because of its importance in establishing one way or the other

what it is going to mean.

DR. HOUN: Could the company please just give us the time line on the completion of that study?

DR. GOTTESNER: We have been working on that study for over two years. We are accumulating patients on the average of about one every two to three months. That is despite the fact that we have looked at sites throughout the whole world in order to find such patients.

It is not easy to do these studies. I just want to make it very clear.

CHAIRPERSON CAMILLERI: I saw Dr. Kelsen's eyebrows move.

DR. KELSEN: What's the design of the trial? I got the PK part of it.

DR. EGORIN: My name's Merrill Egorin. I am serving as a consultant to Merck. University of Pittsburgh was one of the sites chosen to try and get this study done.

It was a very simple drug-drug interaction study, patients getting single-agent docetaxel with aprepitant as the antiemetic. There was really no

incentive for patients to be hospitalized overnight in the GCRC unit.

We tried to get informed consent. We got no patients to sign up for two years. And that was despite taking a fair amount of time sitting and talking with patients.

I also, as long as I am up here, think it is fair to say that just because we went to medical school doesn't mean that people in our family haven't had a malignancy. So I think that is an important thing for consumers to understand.

The other thins is it is sort of an oxymoron. If you have a drug that orally makes you throw up a lot, you are not going to give it to patients. So the orally administered drugs that are coming forward are not highly emetogenic because if they were, you would never be able to give them to anybody.

DR. KELSEN: I was referring to the ones that are going to be given with cisplatin. Those studies are with platinum. They are all being written, and they are all underway.

DR. EGORIN: The reality is if you are looking at approved drugs, we could not get patients with no real benefit to agree to spend two nights in a GCRC away from their families. It is a very, very hard sell.

DR. HOUN: So, Dr. McLeod, I just wanted you to see when you say "pre-approval," there are some difficulties.

DR. McLEOD: Well, I think this speaks to the need for a change in stage design, rather than a lack of need for the data. Within the cooperative groups, we do studies where we do limited sampling. And it is very slow. We all complain about how slow it is going, but it is not that slow.

I think the study design is probably fantastic and so thorough that we can't get people in. I mean, for this sort of study, when we do an institutional study of this sort, we would not be putting patients inpatient. We would be sampling, doing the sampling, in the outpatient facility.

Maybe it is not rigorous enough for what you require. I don't know the answer to that because

certainly we are not submitting our data as part of an FDA application. And so it may be that the rigor is just obstructive to be able to do the study.

I think the issue is still there. I can't remember the wording Ms. Cohen used, but we either have to just throw it out there and see what happens, which is paraphrasing a bit, or try to do these studies.

If it is impossible to do these studies, this drug in my view -- I guess I will be on the record saying this -- looks to be an important advance. I would not want this drug held up for this issue, but Ms. Cohen's point as well as Dr. Egorin's, patients out there, if they are harmed, one will be too many.

CHAIRPERSON CAMILLERI: Dr. Cryer?

DR. CRYER: Right. So, as I remember, I think Ms. Cohen's terminology was "cavalier." Actually, listening to the sponsor, I think that there has been an earnest effort to acquire these patients with these specific combinations.

Your question, Dr. Houn, was, is it our

opinion that the approval should be held up for these additional studies which we are recommending? From my personal perspective, having heard the arguments, I would say the answer would be no primarily because of the advancement that this drug represents compared to the difficulty of acquiring patients in the clinical trial experience.

However, I would like to make what I consider to be an important comment with respect to the post-marketing acquisition of data. And that is that we just don't know what the adverse event profile is going to be with these drugs in combinations with specific chemotherapeutic agents. And in the Phase IV experience, we are going to be dependent upon spontaneous reporting of physicians.

Education, physician education, I think is going to be integral, going to be key to that mechanism. The label is really going to be the only tool or one of the best tools that you have for educating physicians to appropriately alert us as to these potential interactions.

And so with respect to the specific

wording in the label, I did want to bring the discussion to a precautionary section that was in Dr. Della'Zanna's slides, in which it says, "EMEND should be used with caution in patients receiving concomitant medicinal products that are metabolized through CYP3A4. Some chemotherapy agents are metabolized by CYP3A4."

I am not so certain that physicians will know in the walking inventory what those chemotherapeutic agents are that are metabolized via that pathway. And if reporting in the post-marketing experience is going to be important and improve the analysis of this product, I also then would think it would be important to specifically state in the label in that precautionary statement what those chemotherapeutic agents metabolized through that pathway might be.

CHAIRPERSON CAMILLERI: Thank you, Dr. Cryer.

Dr. Metz?

DR. METZ: Yes. I think we are all grappling with the same problem and taking it around

and round in circles. To put it into perspective, I think there is a certain defined 20 percent benefit that we are all very, very comfortable with here and was not an issue for any of us.

We now are getting concerned about a theoretical concern that actually cannot be asked before release. And I think the point is you need to see lots of patients with lots of experience.

Therefore, I would second what has just been said by Dr. Cryer. The label has to say that the testing was done with this particular agent and have had so many patients in and wasn't done with this particular agent and it was done with this particular agent, but it was so few patients. That is the database, which is growing as time goes on.

So you are absolutely correct to raise the concern. I would hate to see the patients who are clearly going to benefit from an important advance limited because of theoretic worries we have about where we want to come down on our votes.

CHAIRPERSON CAMILLERI: And I think, Dr. McLeod, you actually specified at the very end the

same philosophy --

DR. McLEOD: That is correct.

CHAIRPERSON CAMILLERI: -- that this medication should move ahead.

DR. McLEOD: I totally agree. That is not the point I wanted to make with this, but I will reiterate that. I mean, I would love to see those PK studies but not at the expense of slowing down this drug out there.

There may be some patients that end up having some adverse events that weren't predicted. We know that there are going to be patients, a lot of patients, benefitting from this.

The point I wanted to make was if you look at this list of drugs that we were just voting on, only one of them is an oral agent. And that oral agent is not highly emetogenic and also has quite a lot of variability already in its blood levels. That's the imatinib.

So of those agents we are voting on, it is not a big issue. Now, worrying about the future, certainly that is something that has been raised. But

I just wanted to point out for those of you who are not familiar with these agents that only one of them is currently oral. And it is not likely to be a big issue in terms of interaction here.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Brawley?

DR. BRAWLEY: First, I agree with what Dr. Cryer and Dr. Metz said wholeheartedly. And that was part of my comment. I want to speak partially to the consumer community. I see a lot of patients who vomit an awful lot. Even with the drugs that we currently have, they vomit an awful lot. And they need something better. I see here something that sounds like it's better.

Now, we may not have 100 percent assurance that it is absolutely safe at this point, but scientifically to find out that it is 100 percent safe with all of these drug combinations is actually probably impossible.

If you went to the old Soviet Union and dictated that everybody go onto a clinical trial and run a clinical trial of 100,000 cancer patients for 5

years, you are not going to find all the ins and outs, all of the nuances of this drug in combination with other drugs.

I think we have to realize that every drug that is approved has some risk associated with it. I think all of us have seen people die from aspirin.

Thank you.

CHAIRPERSON CAMILLERI: Thank you.

Ms. Hoffman?

MS. HOFFMAN: Yes. As a parent whose child went through BMT pre-5-HT_3 therapy, *et al.*, in 1987, it was hell. I do want to say, too, that I don't want to see this drug stopped. I think there is great value to it. It was horrendous. We are talking vomiting every five minutes day in, day out 24 hours a day.

That said, I do want to see some post-marketing studies done. And I would like to know what steps are being taken? Now that you have done a Phase III trial in adults, what is happening in terms of pediatrics? Are there tests and studies planned? Where are you in that process?

You talked about patient population. We have got COG. And kids are pretty much in-hospital and a cooperative group. So there is a patient population there.

CHAIRPERSON CAMILLERI: Thanks.

Can we have a very brief comment on what other studies are being done in particularly children with cancer?

DR. HORGAN: As we mentioned, this is something that has been actively concerning us. That is why we enrolled a few patients at a specific site in our Phase III program where they had access to a pediatric population. They were very eager to see how the drug would benefit their patients.

We are actively considering pediatric studies with a view to doing a study in adolescent patients initially to assess the efficacy in an adolescent **population getting highly emetogenic chemotherapy.

CHAIRPERSON CAMILLERI: Thank you.

Dr. Fogel?

DR. FOGEL: I agree with Dr. Brawley's

comments regarding the importance of this new drug and the fact that we cannot know with absolute certainly about its safety. I also agree with what he said, that the drug should be released in these post-marketing studies, can be obtained obviously after the drug has been released.

There is just one concern I have. When a new drub comes to market, particularly one that has been shown to be effective, doctors will tend to generalize and expand the indications. You may find that there are doctors who will use this for nausea and vomiting that is not chemotherapy-related.

I make a strong urge to the agency to make sure that this possibility is excluded by specific wording that this drug is only approved for chemotherapy-induced nausea and vomiting.

DR. HOUN: What is the GI experts' view on the potential for off-label use for nausea and vomiting for a variety of GI conditions? Is there anticipation?

DR. LEVINE: Yes. Levine.

I would say definitely yes. And I would

say this is the time on the labeling to put it in bold. The only thing a general practitioner looks at is the bold print usually. And if he is lucky enough to look at that, it must be a small percentage.

I would put something like this in bold print, exactly what we have discussed. I would agree with the post-approval with kinetic studies, pharmacokinetic studies, also.

CHAIRPERSON CAMILLERI: Dr. Metz?

DR. METZ: Yes. I would like to actually support that. And I would agree entirely with Dr. Fogel. Off-label use might be the dangerous situation here. Treating for more than five days might be an issue because of this auto-metabolism and a few other things that were mentioned earlier.

Also, I think we jumped to assume that rescue therapy is -- this drug cannot be used for rescue therapy. That's treating somebody for nausea. I would make sure the label has that this is a prophylactic regimen that is going to be used. It works, and it's safe. There are a lot of problems in terms of patients who are vomiting. It should be

restricted.

Now, do I think that it is going to really be overused? You know, I don't know. I think that clearly if I do an endoscopy on somebody and blow in too much air and they are in the recovery room vomiting, my nurses will come to me and say, "You know, Zofran is good for this." Are they then going to come to me and say, "Hell, EMEND is potentially good for this"? They may.

But I also think that what is out there and what is used for off-label acute, once, uses is probably good enough most of the time. It would be the chronic administration that I think you are really worried about. And I think you must put that in the label.

CHAIRPERSON CAMILLERI: I think I have heard the same message a few times. Any other comments or questions pertaining to the additional information that we're providing to the agency pertinent to question 4B? Do you have any questions from the agency side? Have we addressed this?

DR. JUSTICE: No. I think you have been

very helpful.

CHAIRPERSON CAMILLERI: Okay. Question number 5, does the committee have specific concerns regarding potential drug-drug interactions with other chemotherapeutic agents or other drug classes? Do we think that we have already addressed this during the course of our discussion? Yes, Dr. McLeod, please?

DR. McLEOD: One thing that has been brought up but hasn't been discussed -- and I don't think it needs to be discussed, but it needs to be brought up again -- is the warfarin interaction.

It wasn't clear to me that the INR change that was seen was -- it wasn't clear whether it was clinically relevant or not. And also because it was done in normal volunteers, the dynamics of changes in warfarin metabolism are not always the same as they are in patients, especially elderly patients, with a lot of co-morbidity and co-medication.

So I don't know what is required in that context, but certainly the applicant has done a very nice job in showing that there is an issue there. It will always be flagged in the label, but I think there

may be some post-marketing issues in the context of the age groups in which cancer patients are seen.

So there isn't a lot of warfarin use in childhood malignancy patients, at least from my time at St. Jude, but in the adult side, where the average cancer patient age is 65 to 70, in a general setting like that, there are a lot of people on warfarin and not just for their afib and for their hip replacement, not just for their cancer-induced coagulopathy. And so it will be an issue that needs to be better defined so that someone doesn't get in trouble, as Ms. Cohen mentioned.

CHAIRPERSON CAMILLERI: Other recommendations or comments?

(No response.)

CHAIRPERSON CAMILLERI: Okay. The final part of that question was, if yes, please discuss them. I think we have done that. Are there any other questions or comments that need to be addressed? Any questions, any final questions, from the agency side?

DR. JUSTICE: No. Thanks. We appreciate your work here.

CHAIRPERSON CAMILLERI: On behalf of the agency side, then I would like to thank all of the members, members of the public. I would like to thank the company for the very thorough and clear presentations and our colleagues at the agency, who provided a very good summary and important questions to make sure that if this drug comes on the market and when it does, it is done in as safe a manner as possible. Thank you very much.

We are going to have a 15-minute break. And then we are going to come back for the closed session. Everybody else is excused.

(Whereupon, at 3:03 p.m., the foregoing matter was adjourned and the meeting reconvened in closed session.)