DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

60TH MEETING

Wednesday, January 13, 1999

8:00 a.m.

Holiday Inn Gaithersburg
2 Montgomery Village Avenue
Whetstone Room
Gaithersburg, Maryland

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Glenn Gruett (p.m.)

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John Johnson, M.D. (a.m.)
Robert Justice, M.D.
Robert Temple, M.D. (a.m.)
Ken Kobayashi, M.D. (p.m.)

C O N T E N T S

A.M. Session

C O N T E N T S (Continued)

P.M. Session

P R O C E E D I N G S

Call to Order and Introductions

DR. DUTCHER: Good morning. We will briefly go around the table and introduce the members of the committee.

We will start with Dr. Albain.

DR. ALBAIN: Kathy Albain, Medical Oncology, Loyola University, Chicago.

DR. MARGOLIN: Kim Margolin, Medical Oncology and Hematology, City of Hope, Los Angeles, California.

DR. SCHILSKY: Rich Schilsky, Medical Oncologist, University of Chicago.

DR. SLEDGE: George Sledge, Medical Oncologist, Indiana University.

DR. RAGHAVAN: Derek Raghavan, Medical Oncologist, University of Southern Cal.

DR. PAPADOPOULOS: Essie Papadopoulos, Bone Marrow Transplanter, Memorial Sloan Kettering Cancer Center, New York.

DR. KROOK: Jim Krook, Medical Oncologist, Duluth CCOP.

DR. DUTCHER: Janice Dutcher, New York Medical College.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the committee, FDA.

DR. D. JOHNSON: I am David Johnson, Medical

Oncologist at Vanderbilt University.

DR. MILLER: Carole Miller, Transplant and Leukemia, Johns Hopkins Oncology Center, CBER visitor.

DR. NERENSTONE: Stacy Nerenstone, Medical Oncologist, Hartford Hospital, Hartford, Connecticut.

DR. SANTANA: Victor Santana, Pediatric Oncologist, St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. J. JOHNSON: John Johnson, Clinical Team Leader, FDA.

DR. GRIEBEL: Donna Griebel, Medical Officer, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology Drug Products, FDA.

MS. BEAMAN: I am Carolyn Beaman, Sisters Breast Cancer Network, Consumer Rep to the committee.

DR. DUTCHER: We have a patient representative.

MS. CARROLL: Wilma Carroll, Patient Representative.

DR. DUTCHER: We have a conflict of interest statement to read, please.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: 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 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 a conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

DR. DUTCHER: Thank you.

Open Public Hearing

DR. DUTCHER: There are no speakers that we have been made aware of for the open public hearing.

If that is the case, then, we will proceed with the sponsor's presentation.

NDA 20-954 Busulfex (busulfan) Injection

Orphan Medical, Inc.

Sponsor Presentation

Introduction

Dayton Reardan, Ph.D.

DR. REARDAN: Good morning, ladies and gentlemen, members of the advisory committee, and FDA staff.

[Slide.]

My name is Dayton Reardan and I represent Orphan Medical as head of Regulatory Affairs. Orphan Medical is a company dedicated to the development of orphan drugs, and has had four products approved by FDA over the last three years.

I have been involved with Busulfex since the IND was submitted in 1994. Busulfex is an intravenous formulation of busulfan, which in oral tablet form has been available and marketed since the 1960s.

[Slide.]

Let me review the agenda. Dr. Gary Bream from Lineberry Research Associates will summarize the extensive literature published on the use of busulfan by transplant physicians. The literature review forms much of the basis for the safety and efficacy of busulfan in stem cell transplantation.

He will be followed by Dr. William Vaughan, who was involved in our Phase 1 trial of Busulfex and will discuss its pharmacokinetic profile.

Dr. Borje Andersson, a transplant physician from the University of Texas, M.D. Anderson Cancer Center, and the inventor of this formulation, will present the efficacy and safety data.

Dr. Vaughan will then present his perspective on the benefits and risks of Busulfex in the stem cell transplantation setting.

In addition to those presenting today, the following experts are available to answer questions from the committee or from FDA.

At the request of FDA to be disease-specific in our labeling last May, Orphan Medical proposed this indication for Busulfex with the submission of the NDA. I won't read the complete indication.

The total number of bone marrow transplantation patients in the United States this year will be about 20,000, of whom only about 4,000 would be candidates for a busulfan-based regimen according to current practice.

We do not expect the introduction of Busulfex to change standard practice, but rather to be a substitute for the oral product. This product is a true orphan drug with the potential to be utilized in up to 4,000 patients each year in the United States.

[Slide.]

Shown is the structure of busulfan. It is a

bifunctional alkylating agent known to interfere with DNA replication leading to apoptosis and cell death. Orphan Medical formulates the bulk drug substance fully dissolved in a solution of 33 percent dimethylacetamide and 67 percent polyethylene glycol 400.

When a physician prescribes Busulfex, the pharmacy simply draws up the appropriate amount of solution from the ampule and dilutes it about 10 fold. The diluted product in a 100 mL bag is then infused to the patient over the course of two hours.

[Slide.]

Orphan Medical had very specific and limited goals when this program was first initiated. FDA has provided written and verbal advice and guidance at each step during the development of Busulfex. I would like to acknowledge the FDA staff for their assistance.

Our first step was to determine that there is a real medical need for a intravenous formulation of busulfan. The FDA then agreed that an extensive review of the existing literature would be adequate to demonstrate the safety and efficacy of busulfan when used in transplantation.

Our clinical program was designed to determine the extent to which the intravenous formulation would be better tolerated and more predictable than the oral tablet.

[Slide.]

The requirement for a review of the literature for oral busulfan and the scope of that review was derived from two meetings with the agency. The first of these meetings was a January 16th, 1997, pre-NDA meeting, and the second was a formatting meeting last May.

The FDA minutes from the January meeting stated that it is acceptable that complete and comprehensive literature be provided to evidence the efficacy and safety of oral busulfan as a preparative conditioning therapy for bone marrow transplantation. FDA has subsequently gone to great lengths to verify and come to their own conclusions on the literature.

[Slide.]

This slide shows the clinical trials which have been sponsored by Orphan Medical. There was an initial Phase 1 trial, BUS-2, conducted in 15 patients. Based on these data, we chose a dose of 0.8 mg/kg for the Phase 2 trials.

We then sponsored two, virtually identical trials in autologous and allogeneic patients called BUS-3 and BUS-4. A second pharmacokinetic verification trial, called Amendment 4, completed the data submitted with the NDA.

Ongoing is a pediatric trial at the request of FDA, along with two, small trials at M.D. Anderson Cancer Center. None of these follow-on trials will be addressed

today.

[Slide.]

We intend to show that Busulfex is well tolerated, with an acceptable safety profile. The prospectively designed endpoints were myeloablation and engraftment. Of course, we also followed survival and disease-free survival or relapse.

All of our results are at least equivalent to oral busulfan. We also believe that there are advantages with the use of Busulfex injection versus the oral tablet. An intravenous product is 100 percent bioavailable with reproducible plasma pharmacokinetics, so that each patient is assured of the dose prescribed.

In addition, we found a low incidence of hepatic veno-occlusive disease, and had a very low incidence of early mortality with Busulfex injection in our trials.

[Slide.]

I would now like to introduce Dr. Gary Bream from Lineberry Research Associates. Dr. Bream will review the literature supporting oral busulfan use in stem cell transplantation.

Dr. Bream.

Safety and Efficacy for Oral Busulfan - Indications

Gary Bream, Ph.D.

DR. BREAM: I am going to review the methodology

used for the literature search and to give a brief review of our findings relating to efficacy and safety.

[Slide.]

We have concluded from this review that high-dose oral busulfan has been used successfully in diseases, such as acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, lymphoma, multiple myeloma, and breast cancer.

To ensure that the review was comprehensive, our search included five databases for the search period 1964 through November 2nd, 1997. Keywords used in the search were busulfan, myleran, or the busulfan chemical registry number and transplant preparative regimen or conditioning regimen. The search returned 2,552 citations.

[Slide.]

We systematically reviewed title and abstract information from all 2,552 citations to identify all articles which were specific to the intended use of oral busulfan. To minimize bias, predefined selection criteria were used.

For the first level of selection, papers were eliminated from further review if they focused on detection and treatment of relapse, articles addressing measurement of engraftment or marrow treatment, foreign language articles, articles describing small numbers of patients, and review

articles.

This resulted in 577 relevant articles which described a total of 14,114 patients who had all received oral busulfan as part of their preparative therapy. These 577 articles were reviewed and demographic, dosing, adverse event, and engraftment data were collected in an electronic database referred to as the "Overall Database."

Further selection from this group of 577 papers was conducted again based on predefined criteria. We selected papers that reported on engraftment as this corresponded to the primary endpoint of the Busulfex clinical studies.

Also, an apriori statistical analysis indicated that a minimum of 23 patients would need to be described to ensure that the engraftment data reported was statistically meaningful.

Forty-three articles meeting these criteria were identified which described a total of 2,197 patients; 7 of these 43 papers described comparisons of oral busulfan-containing preparative regimens with those containing total body irradiation.

Only 5 of these 7 provided disease-specific comparisons for efficacy parameters of survival and disease-free survival. Three of these 5 were randomized controlled studies and 2 were retrospective controlled studies.

FDA conducted its own literature search and found 11 additional articles, 10 of which were added to the electronic reference database after our search was completed. This provided us with confidence that our literature search was indeed comprehensive.

FDA also considered in its efficacy assessment 16 papers which we identified, but did not include in our assessment. These papers were not included because they did not meet our specific selection criteria.

In my next five slides, I will present the data from the comparative studies regarding these disease-specific indications.

[Slide.]

In papers describing patients with AML combined without regard to the disease status, the only randomized controlled study was for allogeneic transplants. This paper found no statistically significant difference in disease-free survival between a BuCy2 regimen and a TBI-containing regimen.

Two papers provided retrospective analyses of AML patients receiving autologous transplants. Neither found a statistically significant difference in overall survival or disease-free survival between either a BuCy4 or a BuCy2 regimen and TBI-containing regimens.

[Slide.]

In the subset of patients with AML in first complete remission, two randomized trials explored the efficacy difference of a BuCy2-containing regimen with the TBI regimen in patients receiving an allogeneic transplant.

Ringden found no statistically significant difference in disease-free survival between the two regimens although the trend favored busulfan.

Blaise found a statistically significant difference in both overall survival and disease-free survival which favored TBI. Edward Copelan noted, however, in the 1992 review article, that the survival estimates observed for TBI in this study were higher than normally seen.

The third paper provided a retrospective comparison of the BuCy4 regimen to TBI and autologous transplant recipients. Again, no statistically significant difference was observed in disease-free survival.

[Slide.]

For patients with AML past .01, two papers provided retrospective analyses of either a BuCy4 or a BuCy2 regimen versus a TBI regimen. Dusenberry found a statistically significant difference in disease-free survival which favored TBI, while Selvaggi saw a disease-free survival trend which favored BuCy2, but this difference was not statistically significant.

[Slide.]

Two papers provided data from randomized studies in CML patients. Both compared the BuCy2 regimens to TBI in patients receiving allogeneic transplants. Ringden found no statistically significant difference in disease-free survival cohorts which contained both high- and low-risk CML patients.

Two studies addressed outcomes in chronic phase patients only. Neither observed a statistically significant difference in either overall survival or disease-free survival.

[Slide.]

A single paper compared the effectiveness of a BuCy2 regimen to TBI in a randomized study in patients with ALL. This paper found no statistically significant difference in disease-free survival between the regimens in either the overall group of ALL patients or the subgroup of patients treated in first remission.

This concludes my presentation of information available in the controlled studies. I would now like to review the information that was available from the subset of 43 papers that described patients who had receive bone marrow transplant.

[Slide.]

This slide summarizes the key hematological events

following conditioning with oral busulfan. The main points I would like to make from this slide are that busulfan is myelosuppressive with a range of median times to neutropenia from 4 to 6 days, and a range of duration of neutropenia from 7 to 11 days, also, up to 95 percent of patients engrafted whether you look at either the overall database or the subset database.

[Slide.]

This slide summarizes the disease response to therapy for patients with overt disease, which are all summarized from the subset database. The blue indicates patients who had a complete response to therapy, the yellow, patients who had a partial response, and the red, patients who had no response. Data are reported for the disease categories of AML, ALL, CML, multiple myeloma, lymphoma, and breast cancer.

The next three slides plot the probability of disease-free survival versus time as reported in these 43 papers.

[Slide.]

The first slide shows the data for patients with acute myelogenous leukemia. For low-risk patients in first complete remission, the majority of papers reported disease-free survival probabilities in excess of 40 percent. The highest reported value was 85 percent in two years.

High-risk patients transplanted beyond CR1 or with primary refractory disease had poor outcomes as would be expected. Disease-free survival probabilities generally were below 40 percent, ranging from a low of 7 percent to a high of 48 percent. All but the lowest reported value of 7 percent fell between 24 and 48 percent.

The wide acceptance that transplant represents the only curative option for these patients is reflected in the routine inclusion of it in the standard medical textbooks, such as DeVita. The data for chronic myelogenous leukemia are presented on the next slide.

[Slide.]

CML patients in chronic phase had disease-free survival probability estimates in excess of 50 percent, ranging from 58 to 71 percent. Higher risk patients beyond chronic phase had 3 or probability estimates of 25 and 41 percent.

As Deisseroth wrote in the same DeVita text, expected 5-year disease-free survival estimates for patients with CML in chronic phase following allogeneic transplant range from 40 to 70 percent, or for patients beyond chronic phase, they range from 10 to 30 percent.

[Slide.]

For patients with multiple myeloma, ALL, MDS, and lymphoma, the range of Kaplan-Meier probabilities of

disease-free survival in our 43-paper subset ranged from 20 percent to 74 percent reported at an interval of 1 to 4 1/2 years.

[Slide.]

I would like to address the safety of oral busulfan based upon a review of the adverse events as reported in the literature.

I would like to draw your attention in particular to VOD and seizures, both recognized consequences of the use of oral busulfan. Veno-occlusive disease occurred in 13 percent of patients overall with nearly identical frequency in the autologous and the allogeneic transplant groups.

Seizures occurred in 3 percent of patients with nearly equal frequencies between the two groups. Busulfan-induced seizures could be adequately controlled, however, with prophylactic administration of anticonvulsants.

The next slide lists the primary causes of death following transplant.

[Slide.]

Most deaths were the result of relapse or disease progression, GVHD, infection, or other treatment-related causes. For regimen-related events, VOD was the most frequent cause of death, occurring at a frequency of 5 percent.

Acute mortality, which is death from all causes

less than or equal to 30 days post-transplant, ranged from 2.6 percent in the autologous transplant patients to 7.9 percent in the allogeneic transplant patients.

[Slide.]

To summarize, in our selected literature review, over 14,000 patients were reported to have received oral busulfan as part of their conditioning therapy prior to bone marrow transplant.

Our search found that regimens containing 16 mg/kg oral busulfan were myelosuppressive. Engraftment occurred in up to 95 percent of patients in median times which ranged from 8 to 42 days.

Oral busulfan has been used successfully as part of the transplant therapy to treat diseases, such as acute and chronic myelogenous leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, lymphoma, both Hodgkin's and non-Hodgkin's, multiple myeloma, and breast cancer.

In regards to safety, mucositis, fever, nausea/vomiting, rash, and diarrhea occurred frequently. The VOD occurred in 13 percent of patients, while seizures occurred in 3 percent of patients, but could be lowered with prophylactic anticonvulsive therapy.

The frequency of acute mortality was 7 percent overall.

Thank you.

DR. REARDAN: I would now like to introduce Dr. William Vaughan, who participated in the Phase 1 study of Busulfex and helped to design the Phase 2 programs. He is Director of the Bone Marrow Transplantation Program at the University of Alabama, and will be speaking to you about the kinetic data assembled during the course of this NDA.

Dr. Vaughan.

Pharmacokinetic Comparison of IV Busulfex Versus Oral Busulfan

William P. Vaughan, M.D.

DR. VAUGHAN: Thank you, Dr. Reardan.

[Slide.]

What I would like to do in the next few minutes is to examine the pharmacokinetics of Busulfex as determined in these trials in the context of the goals of the preparative regimen in bone marrow transplantation and the pre-existing data on the pharmacokinetics of oral busulfan.

The goal of bone marrow transplant preparative therapy is to take advantage of the hematopoietic rescue, to escalate dose to achieve disease eradication, and facilitate engraftment with acceptable mortality.

Busulfan is a drug that is widely used in transplantation. It can be given in up to 100 times its minimum effective dose before fatal non-hematopoietic toxicity is encountered.

The published pharmacokinetic data on high-dose oral busulfan demonstrates a wide variation in level achieved versus dose given. This graphic illustrates the problem with this variability. A wide CV or standard deviation of this curve creates an unacceptable tradeoff between too much relapse and too much mortality.

This is not just a theoretical concern since the level of drug exposure has been identified above which an unacceptable rate of hepatic veno-occlusive disease occurs.

[Slide.]

VOD is a serious regimen-related toxicity of high dose cytotoxic drugs and radiation therapy. Dr. Louise Grochow and colleagues first reported the association of high busulfan AUC with veno-occlusive disease in 1989. Using an HPLC technique for determining plasma concentration, she reported that the first 1 mg/kg dose of the standard 16-dose schedule produced a mean AUC of 2012 micromolar minutes with a standard deviation of 1223.

Now shown on this slide but worth mentioning was that the range was from 606 to 5144 micromolar minutes. A scattergram suggested a major increase in VOD risk at approximately mean plus 1 standard deviation, 3235.

Dr. Grochow subsequently reported, using a different assay, that the VOD risk threshold was 1500. Using a similar modification of her original HPLC assay, Dr.

Dix and colleagues reported a mean busulfan AUC of 1304 with a standard deviation of 380 for busulfan first-dose pharmacokinetics, and confirmed the utility of the 1500 micromolar minutes VOD cutoff.

The other major acute toxicity of high dose busulfan is seizures. The studies of Vassal and colleagues suggested that the association with seizures after high dose busulfan administration appeared to result from CNS penetration of the drug and correlated with administered dose.

[Slide.]

With these considerations in mind, we conducted a pilot study of Busulfex with a Phase 1 design. The first dose was the intravenous Busulfex formulation, and doses 2 through 16 were oral busulfan in the standard BuCy2 preparative regimen.

The intravenous dose was escalated according to the schedule shown here, and administered over 2 hours to mimic the time to Tmax reported by others for oral administration. Three patients were treated at each dose, and 3 additional patients were treated at the 0.8 mg/kg dose.

Oral busulfan was given in the standard, 1 mg/kg every 6 hour schedule beginning 6 hours after the intravenous Busulfex dose.

The target AUC for busulfan was taken from Dr. Grochow's original work in the original protocol, and was stated to be 2000 plus or minus 1200 micromolar minutes.

Plasma pharmacokinetics were studied following the intravenous Busulfex at dose 1 and after dose 5, the fourth oral busulfan dose.

These were both early morning doses, thus facilitating multiple sample collection and avoiding any chronopharmacologic consideration.

Busulfan levels were assayed by HPLC.

[Slide.]

The slide represents graphically the individual patient AUCs from all 6 of the patients with completely evaluable data from both the I.V. and oral preparations, 6 I.V., 6 oral.

The dark blue bars in the oral grouping represent the 3 fully evaluable patients dosed at the 0.8 mg/kg I.V. Busulfex dose and are in the same order of presentation. The interpatient variability seen with the oral drug is considerable, with 3 patients exceeding the presumed VOD risk threshold of 1500 micromolar minutes.

[Slide.]

The mean first dose busulfan AUC after dose 1 Busulfex, given at 0.8 mg/kg is shown on this slide, and was 1180 micromolar minutes with a range from 943 to 1472. Time

to peak busulfan concentration after oral dosing was at a mean of 1.8 hours with a median of 2 hours, thus validating the 2 hour infusion time for the I.V. dose.

No acute toxicity was recognized during the Busulfex infusion.

On the basis of these data, the 0.8 mg/kg dose was selected for the Phase 2 study.

[Slide.]

The definitive pharmacokinetics study was organized as an amendment to the Phase 2 trials. This study included 12 patients meeting the entry criteria for BUS-3 and BUS-4 and represents the reverse design of BUS-2. The patients received their first dose as oral busulfan at 1 mg/kg, and doses 2 through 16 as the 2-hour infusion of Busulfex at the dose of 0.8 mg/kg.

Pharmacokinetics were assessed after the first dose, which was oral, and after the ninth dose, which was the eighth I.V. dose. As in BUS-2, these were both early a.m. doses to avoid chronopharmacologic differences. Peak and trough measurements were obtained on dose 13.

An improved GC-MS analytic technique was used for these plasma drug concentrations, and these were performed in the analytic laboratory at the Fred Hutchinson Cancer Research Center.

[Slide.]

Blood was collected immediately before the first dose, which was oral, and then every 15 minutes through 90 minutes, and then at hours 2, 4, and 6, the 6-hour dose being immediately before the commencement of the first Busulfex dose.

To establish Busulfex pharmacokinetics, blood collections were made immediately before the commencement of the dose 9 infusion and then, as indicated on the slide, during post-infusion.

The Cmax level was determined by blood collection 5 minutes prior to the end of the 2-hour infusion, and trough level determined immediately prior to commencement of the next infusion, at the 6-hour time point.

Peak and trough levels were collected at dose 13 with blood collection immediately before the dose 13 infusion to establish the trough, and blood collection 5 minutes before the end of the 2-hour infusion to establish the peak.

[Slide.]

This slide indicates the pharmacologic parameters measured for the first dose, the oral busulfan. It is important to note that AUC calculations could not be made on the three patients highlighted.

Two of these patients had significantly delayed absorption as indicated by the prolonged Tlag. In these two

patients, plasma concentrations were still increasing at 6 hours, making AUC calculations impossible.

The third patient had already begun dose 2 infusion prior to drawing the 6-hour level, and so it also could not be analyzed.

The mean Cmax of 870 ng/mL, shown here, was reached at a mean of 2.76 hours, and the mean AUC equaled 1396, but with considerable variation as shown by the large standard deviation.

[Slide.]

Because Busulfex is an intravenous preparation, all patients at dose 9 were fully evaluable, but for accurate comparison with the oral, the same three patients are excluded. The mean Cmax of 1167 is higher than the oral Cmax, but this is expected because the dose 9 infusion is superimposed on a residual steady-state level.

The mean AUC is corrected for the steady-state assumption, and was 1156. Note the relatively small standard deviations for all the I.V. Busulfex parameters.

[Slide.]

The following slides illustrate the individual patient data between doses for the 9 fully evaluable patients. The first plot of individual AUCs at dose 1 and 9 clearly indicates the tighter data set following Busulfex, the Busulfex dose 9, oral busulfan dose 1.

[Slide.]

This slide shows the peak levels at dose 9 and 13, indicating the intrapatient predictability of plasma levels for the Busulfex preparation.

[Slide.]

This next slide shows that a predictable relationship also exists between the trough levels.

[Slide.]

On this slide, we see the individual patient plasma concentrations plotted against time after the first oral dose. The red lines connect the data for the three inevaluable patients. The variation in absorption is clearly seen in both the Tlag and Tmax.

The two patients inevaluable because of increasing plasma concentrations at the 6-hour time point can also be clearly seen, as well as the data on the patient who had a peak at 4 hours and then had the 6-hour level drawn after the start of the second infusion.

[Slide.]

The individual patient concentration versus time profiles for Busulfex are shown here. You can see the much more ordered profiles resulting from the predictable I.V. administration of the Busulfex formulation.

[Slide.]

This table summarizes the results of the

pharmacokinetics from Amendment 4. It highlights the predictability conferred by the 100 percent bioavailable Busulfex with reduced standard deviation for every parameter - Cmax, Tmax, oral, I.V., T1/2, oral, I.V., and AUC, oral and I.V. Note particularly, of course, the Tmax.

[Slide.]

To summarize the Amendment 4 results, Busulfex avoids variable bioavailability. There is no delayed absorption. There is no loss due to vomiting. All Busulfex doses are evaluable and demonstrate the potential for limited sampling pharmacokinetics. Busulfex pharmacokinetics are more uniform. This study supports Busulfex dosing at 0.8 mg/kg as a 2-hour infusion.

I would now like to show you the pharmacokinetic data collected on the other 103 patients enrolled in the pivotal BUS-3 and BUS-4 trials.

[Slide.]

In these pivotal Phase 2 studies, Busulfex was dosed at 0.8 mg/kg, has a 2-hour intravenous infusion every 6 hours for 16 doses. Blood was collected at dose 1 and dose 9 as indicated to enable pharmacokinetic calculations. 98 of the 103 patients in these studies were evaluable for all pharmacokinetic parameters for dose 1 and for dose 9.

Peak and trough levels, as previously described, were again collected on dose 13.

[Slide.]

The results of this very extensive pharmacokinetic assessment are summarized here. Plasma busulfan values were again determined using GC-MS, and noncompartmental methods were applied to determine the pharmacokinetic parameters.

Cmax for the first I.V. dose was proportionately lower than that for dose 9, with a consistency in AUC calculations. This is the Cmax as expected because of the residual steady-state level prior to dose 9. The AUC calculations, very consistent.

Hence, Busulfex injection provided predictability of time to peak concentration, reproducibility of steady-state concentration, and AUC, and outstanding standard deviation around the mean pharmacokinetics parameters.

[Slide.]

The next two spaghetti plots give additional supportive evidence of the intra- and inter-patient predictability of the pharmacokinetic parameters measured for Busulfex.

In this first plot, the relationship of the AUC measured at dose 1 and dose 9 is shown for all 98 patients. The red lines are the BUS-3, autologous transplant patients, and the blue lines are the BUS-4 patients.

As you can see, there is a strong linearity in the relationship. Ninety percent of all patients maintained AUC

at doses 1 and 9 below the level of 1500, the level associated with significantly increased risk of veno-occlusive disease.

[Slide.]

This slide shows that the same relationship holds true for the peak levels seen in these plots for all of the BUS-3 and BUS-4 patients, the peak levels for dose 9 and dose 13, steady-state is achieved and maintained.

[Slide.]

In conclusion, these data confirm and extend the results of Amendment 4. Busulfex avoids variable bioavailability. There is no delayed absorption, no loss due to vomiting. All Busulfex doses are evaluable potentially by limited sampling analysis.

Intra- and inter-patient consistency exists for dose 1, 9, and 13. This data supports the dose of 0.8 mg/kg by 2-hour infusion. It should be noted that patients in these protocols were treated with a multitude of concomitant medications including antiemetics, antifungals, anticonvulsants, antibiotics, and yet the pharmacokinetics of Busulfex within individual patients remained relatively constant for each dose from dose 1 to dose 9 to dose 13.

These data collectively demonstrate that the pharmacokinetic profile of Busulfex is superior to oral busulfan based on the fact that it is 100 percent

bioavailable, levels are predictable within and between patients, and the profile will be easier to monitor through limited sampling strategies.

I further believe that the pharmacokinetic data presented supports the dose of 0.8 mg/kg by 2-hour intravenous infusion.

[Slide.]

I would now like to introduce Dr. Borje Andersson, Professor of Medicine and Hematology, a transplant physician at the University of M.D. Anderson Cancer Center, who will present the clinical data.

Safety and Efficacy of Busulfex

Borje S. Andersson, M.D., Ph.D.

DR. ANDERSSON: Good morning.

I am going to describe the pivotal two studies known as BUS-3 and BUS-4 this morning. These studies had identical protocols with the difference being the source of the transplanted cells.

In BUS-4, they were from HLA-matched sibling donors. Further, the BUS-4 patients received immunosuppressive therapy post-transplant according to institutional guidelines. Supportive care included drug combinations of low-dose methotrexate with either cyclosporin or tacrolimus or FK-506.

[Slide.]

The stated protocol objectives were to deliver Busulfex as scheduled, to document engraftment, monitor toxicities, and measure plasma pharmacokinetics.

[Slide.]

This is the study design where Busulfex was administered between days -7 and -4 followed by 2 days of cyclophosphamide days -3 and -2, then following a day of rest with the graft being infused on day zero.

There were three study periods as shown, the first, acute phase period lasting from day -7 at the start of Busulfex until day 28 post-transplant, at which time the patients were restaged and then there was a short-term post-study surveillance phase from day 29 through day 100, followed by a long-term post-study surveillance phase.

[Slide.]

Five study sites participated in the BUS-3 study and 7 in the BUS-4 study.

[Slide.]

On this slide, you can see the disease inclusion criteria covering patients with advanced hematologic and malignancies.

[Slide.]

On this slide are the patient eligibility criteria which are pretty much standard for this type of study.

[Slide.]

The dose was calculated on the basis of actual, ideal or adjusted ideal body weight according to institutional practice. All Busulfex doses were prepared by the site pharmacies to a final concentration of approximately 0.5 mg/mL for busulfan for controlled rate infusion, and prophylactic phenytoin and antiemetics were given per institutional guidelines.

[Slide.]

These were the BUS-3 and BUS-4 myeloablation and engraftment endpoints. These are standard definitions for bone marrow transplantation studies, and engraftment at the time of recovery of neutrophil count up to 0.5 x 10^9/L.

[Slide.]

Here are the demographics by disease. Most of the patients in the BUS-3 study had lymphoma, and in the BUS-4 study, most patients had leukemia. While not shown on this slide, it should be noted that in the BUS-3 study, 40 percent of the patients were over age 40, and in BUS-4, almost half, or 48 percent, fell in that age range.

The ethnic racial distribution reflected the overall population of patients at the participating transplant centers.

[Slide.]

Disease status at the time of transplant is an important variable affecting outcome. Evaluation of outcome

by diagnosis-specific classifications was performed in select disease categories and some subgroups. Patients transplanted with active disease represented 83 percent in BUS-3 and 75 percent in BUS-4, and overall it was 79 percent.

[Slide.]

To be heavily pretreated was defined as meeting at least one of the following criteria: a minimum of three prior chemotherapy regimens, prior radiation therapy, or a previous bone marrow transplant. Sixty-three percent of the patients in both studies met this definition, 81 percent of the patients in BUS-3 and 48 percent in BUS-4, and for 11 patients, this was their second transplant.

[Slide.]

This slide shows the dynamics of myeloablation and engraftment. All 103 patients became neutropenic following BuCy at a median onset of 4 days post-transplant for both trials.

The median duration of neutropenia was 6 days, ranging from 2 to 13 in BUS-3, and 9 days ranging from 1 to 28 days in BUS-4. All evaluable patients engrafted with slightly delayed engraftment in BUS-4 compared with BUS-3 due to the use of low-dose methotrexate as part of the post-transplant graft versus host disease prophylaxis regimen.

[Slide.]

The primary efficacy parameter in both protocols was engraftment defined as the day the absolute neutrophil count exceeded 0.5 x 10^9/L. All 42 or 100 percent of the patients engrafted in the autologous group. The median time to engraftment was 10 days, ranging from 8 to 19 days post-transplant.

[Slide.]

In BUS-4, all evaluable patients, 60 of them, engrafted. One patient died of pneumonia before engraftment could be evaluated. The median time to engraftment was 13 days, ranging from 9 to 29 days.

[Slide.]

RFLP analysis or cytogenetics were not available to document engraftment on 6 patients. These studies were indeterminate for 11 patients, and were evaluable for the remaining 43 patients on BUS-4. Of these 43 patients, 38 showed complete chimerism and 5 showed mixed chimerism. That was reflective of persistent or recurrent active disease at the time of sampling.

[Slide.]

This slide summarizes the efficacy data seen with Busulfex. These are the literature data using high-dose oral busulfan. Both regimens are highly efficacious in achieving the primary goals of myeloablation and engraftment. Of particular interest is low regimen-related

mortality in the first 28 days, and the overall treatment-related mortality in the first 100 days with Busulfex.

This comparative data for oral busulfan was taken from contemporary publications from 1993 to the present time, attempting to include only patients representing the currently used supportive care regimens.

[Slide.]

This slide demonstrates the survival and disease-free survival for patients in the allogeneic study. The disease-free survival at one year is 42 percent. The treatment-related mortality from all causes other than relapse is only 10 percent, and further, the overall survival at one year is still close to 70 percent in this group of high-risk patients.

[Slide.]

The BUS-3 autologous study is a somewhat clearer study regarding safety since there is not the confounding immunologic impact of the allogeneic graft and the immunoprophylactic post-transplant regimen.

It is extremely encouraging that the 100-day mortality is zero. The overall one year survival is 70 percent and the projected disease-free survival is 56 percent.

The next set of slides will address disease-specific efficacy measures defined in the protocol as day 28

outcomes.

[Slide.]

The antitumor effects of Busulfex were considered separately in the disease categories representing the largest patient cohorts.

In BUS-4, we have analyzed CML and AML, and in BUS-3, the lymphoma disease groups. Of 17 CML patients, 4 were considered in chronic phase at the time of transplant. All 4 achieved a complete remission; 13 patients were transplanted in either accelerated or blastic phase, 12 achieved a complete remission and 1 failed.

[Slide.]

Patients with either AML or myelodysplastic syndrome receiving allogeneic transplants are included in this evaluation. Twenty-six patients had AML and 9 had myelodysplasia. Eight patients were transplanted in first remission and were considered standard risk for outcome and serious toxicity. All other patients were considered high risk.

All 8 patients transplanted in first remission remained in remission post-transplant, and in the high-risk AML group, 15 of 18 achieved a complete remission, 2 failed, and 1 patient died from complications of pneumonia in the acute study period.

Of particular interest here to us is the

myelodysplasia group where we transplanted 9 patients. All 9 achieved a complete remission, and as of July 31, '98, 15 of the 32 responders remained in complete remission. The median follow-up at that time was 9 months, ranging from 6 to 20 months.

[Slide.]

In BUS-3, the outcome for patients with non-Hodgkin's lymphoma and Hodgkin's disease were analyzed separately. The non-Hodgkin's lymphoma group was a high-risk population where 5 of 11 patients were refractory to conventional chemotherapy. One patient had chemotherapy, untested relapse. One patient was in the second remission, and 4 patients were in the partial remission after salvage chemotherapy.

Of these 11 patients, 10 achieved a clinical remission with the transplant, and 1 progressed through the treatment. There were no early deaths. The one refractory patient died of disease progression on BMT day plus 285. As of the safety update on July 31 of '98, 9 of the 10 responders remained in clinical remission with a median follow-up of 7 months, ranging from 4 to 20 months.

[Slide.]

For Hodgkin's disease, all 24 patients that received an autologous transplant on BUS-3 were considered high risk. They all achieved a clinical remission with 50

percent being alive and in a continued clinical remission with an average follow-up of 11 months, ranging from 1 to 18 months. Twelve patients have relapsed. Of these, 9 are alive and 3 died between 4 and 7 months post-transplant.

Outcomes in autologous transplantation for lymphoma rely heavily on the preparative therapy for the antitumor effect. Despite advanced disease status in the majority of these patients, the clinical outcome so far is comparable, if not improved, over published reports with alternative regimens.

The following slides will address the safety of Busulfex from BUS-3 and BUS-4.

[Slide.]

This will show a low incidence of early serious treatment-related toxicity and mortality. All 103 patients completed the 16-dose Busulfex regiment, and no unique toxicities were identified with the I.V. formulation.

Thus, the adverse event profile is consistent with that seen with oral busulfan when used in high-dose pre-transplantation conditioning therapy.

[Slide.]

Obviously, the most serious adverse event is a patient's death. As stated before, we believe that the autologous group is the most representative for regimen-related toxicity because of the absence of an allogeneic

effect and treatment, and to day 100 it is most noteworthy that there were no deaths in the autologous patient cohort.

The deaths in the allogeneic patient population will now be examined in detail.

[Slide.]

Through BMT day +28, there were two deaths. Both of them were due to infection. Between day 29 and day 100, there were six additional deaths. Two patients died from hepatic veno-occlusive disease, 1 patient died from pulmonary fibrosis, 1 developed alveolar hemorrhage secondary to pneumonia, and 2 have progressive disease. In all, we consider that 4 were possibly regimen related.

[Slide.]

Following the day 100, there were 3 deaths due to graft versus host disease, 5 deaths due to infection, 10 deaths due to disease progression. There were no late deaths that could be attributed to regimen-related toxicity.

[Slide.]

For non-hematologic serious adverse events, 84 percent of the patient experienced none or 1 SAE, and the remaining 16 percent experienced 2 to 4 SAEs.

[Slide.]

The serious adverse event profile for the various non-hematologic organ systems is qualitatively equivalent to that seen after high-dose oral busulfan. We will therefore

examine in detail only pulmonary, CNS, and hepatic SAEs. These are the recognized dose-limiting toxicities for high-dose oral busulfan.

Of the 4 pulmonary SAEs which occurred, only the one case of possible pulmonary fibrosis could be potentially attributed to Busulfex. This patient had had prior mantle irradiation for Hodgkin's disease, and he had also been extensively exposed to bleomycin.

[Slide.]

One patient suffered agitation, combativeness, and disorientation reported as possibly related to Busulfex, however, the patient was also receiving concomitant psychotropic medications.

Another patient had what was described as a brief seizure during the second day of cyclophosphamide administration more than 36 hours after the last dose of Busulfex. This patient had had difficulty keeping down the prophylactic phenytoin, and received I.V. phenytoin acutely in connection with this episode. The seizure lasted less than one minute, and did not recur after the prophylactic phenytoin had been supplemented intravenously.

[Slide.]

Hepatic veno-occlusive disease is the most serious and dose-limiting adverse event after high-dose alkylating agent regimens, and it is also seen after total body

irradiation. Its reported incidence varies, but it is more frequently seen in heavily pretreated patients, and the mortality risk is high for moderate and severe forms of VOD.

A recently published meta-analysis of BuCy preparative regimens reported an incidence of about 9 percent.

[Slide.]

This slide summarizes the patients on the current studies considered by the respective site investigator to have clinical veno-occlusive disease post-transplant. Only 4 of these patients fulfill the Jones criteria.

As can be seen, 2 patients had a previous bone marrow transplant, and they were all considered as heavily pretreated based on the previously described criteria.

[Slide.]

If we only consider first transplant patients, the mortality from veno-occlusive disease is 1 percent. Second transplant patients appear to have a slightly higher incidence and mortality.

Since all patients who developed clinical signs compatible with VOD were heavily pretreated, we should try to delineate discrete risk factors that might predispose for this complication.

[Slide.]

The superior pharmacokinetic profile of Busulfex

reduced the contribution of busulfan AUC to the risk of VOD such that other factors became evident. This slide shows the combined contribution of busulfan AUC and prior irradiation.

Patients with no prior irradiation therapy had an incidence of VOD of only 1 out of 41 or 2.5 percent. Patients with prior irradiation and an AUC below the median had no VOD, but 4 of 9, or 44 percent, who had received prior irradiation and had an AUC above the median, developed clinical veno-occlusive disease post-transplantation.

[Slide.]

In summary, we conclude that there were no new safety concerns identified in the clinical studies with Busulfex.

Secondly, the AE profile consisted of well-described events commonly encountered during hematopoietic progenitor cell transplantation.

Thirdly, there was a low incidence of VOD, a total of 6 patients, or 5.8 percent, in the combined studies.

Fourth, there was a low overall mortality through day +100 post-transplant.

[Slide.]

Conclusions. 1. Busulfex injection is efficacious and safe as pretransplantation conditioning therapy. It allows administration of a precise dose. It

provides greater predictability in achieving the targeted therapeutic window.

Its bioavailability is unaffected by emesis. It eliminates the variability in absorption, and it eliminates the hepatic first-pass effect.

[Slide.]

2. The administration of drug was well controlled and the incidence of VOD was low.

3. The toxicity profile of Busulfex consisted of well described events that are familiar to transplant physicians.

4. Use of Busulfex will not require new support strategies.

5. Busulfex enhances the ease of administration.

I want to thank you for your attention and then we will go back to Dr. Vaughan.

Benefit and Risk Summary

DR. VAUGHAN: Thank you, Dr. Andersson.

I would now like to spend just a few minutes providing my perspective on the Busulfex data you have seen.

[Slide.]

First, I believe that the literature search described by Dr. Bream demonstrates that busulfan has been, and continues to be, an important part of effective regimens for pretransplant conditioning in bone marrow

transplantation.

There are relatively few trials of the elegance that we would like in the ideal world, but the extensive and sustained record of publication and clinical experience underscores the increasing importance of busulfan in the transplant setting for a variety of indications.

[Slide.]

Myeloablative therapy with bone marrow transplantation has gradually become established treatment for hematologic malignancy, marrow failure states, and selective solid tumors.

For specific subsets of patients with AML, CML, ALL, non-Hodgkin's lymphoma, and myelodysplastic syndrome, it is clearly established as a curative therapy. These are the patients for whom Busulfex is especially appropriate. Among these diseases, non-Hodgkin's lymphoma is the only one in which busulfan-based regimens have been infrequently reported in the past, but the rate of reports for this indication are increasing.

[Slide.]

As the literature reflects, oral busulfan is widely used today in both allogeneic and autologous transplant conditioning regimens despite there being serious drawbacks to the available 2 mg tablet.

As I demonstrated earlier, there is inter-patient

pharmacokinetic variability that results from differences in absorption complicated by emesis. The emetigenic nature of the drug and the requirement to take excessive numbers of tablets on a frequent schedule while nauseated often results in loss of an indeterminate portion of each dose.

The medical consequences of this are significant. Overdosing can result from pharmacokinetic variability and from replacement of inaccurate estimates of lost tablets. Hepatic VOD is demonstrated to be associated with excessive exposure to busulfan. Underdosage by poor absorption or inadequate replacement increases relapse risk.

[Slide.]

The advantages of Busulfex over oral busulfan are summarized in this slide. Pharmacokinetic parameters are predictable and not subject to variable absorption and inadvertent drug loss due to emesis. The delivery of all doses is assured. In these studies, 100 percent of patients received 100 percent of their intended doses of Busulfex.

While assured delivery is not a pharmacokinetic parameter, imprecise delivery creates variable and often inevaluable pharmacokinetics. The exposure of the liver to high concentrations of busulfan and plasma due to the "first pass" effect following oral administration is eliminated. This may contribute to the low incidence and possibly less severe VOD seen in these studies. No patient in these

studies failed to engraft.

[Slide.]

Does the Busulfex formulation carry any risks that would argue against its use as a substitute for the oral drug despite the pharmacokinetic and patient tolerance benefits? The answer is no.

In the safety database, over 100 patients, each receiving 16 doses of Busulfex, no new toxicities over oral busulfan were seen. Moreover, there was no increase in the frequency or severity of any toxicity compared to that reported for oral busulfan. Specifically, there was no toxicity related to the vehicle or to the infusion itself.

[Slide.]

Finally, Busulfex provides a great advantage from a convenience standpoint for patient and nurse. It is hard to even compare the experience of a 70-kilogram person taking 35 pills of an emetigenic drug every 6 hours with the experience of simply receiving an intravenous infusion through an existing central venous catheter.

[Slide.]

Let me close with a personal perspective. Busulfex is a drug that we in the transplant community really need. Those of us who are familiar with the use of oral busulfan have long recognized its significant limitations.

I believe there should be no doubt about the medical need for the intravenous formulation Busulfex. The 100 percent bioavailability and dose assurance of Busulfex alone justifies this statement. The ability to do reliable pharmacokinetically directed therapy for these high-risk procedures easily and in every case is a major added advantage.

Finally, I would like to say a word about the indication. The indication for Busulfex needs to be broad since all of the standard conditioning regimens for allotransplantation, for a variety of small incidence diseases, are either busulfan based or utilize TBI.

Many times total body irradiation is either unavailable or unable to be used because of prior irradiation or other factors associated with increased risk.

If Busulfex is necessary for relatively common indications within this orphan category, it is certainly necessary for some of the less common indications.

Thank you.

DR. DUTCHER: Thank you, and thank you for a very elegant pharmacokinetic study. It was very nice to see that kind of data.

We now have a period of time for questions to the sponsor from members of the committee.

Dr. Papadopoulos.

Questions from the Committee

DR. PAPADOPOULOS: A question for Dr. Vaughan or Dr. Andersson. It was unclear to me -- this is just a point of clarification -- although there were several sites obviously involved in the trial, and there was site preference as to the use of actual body weight, ideal body weight or adjusted body weight, there were some outliers. I mean the data appeared tight, but approximately 10 percent were above the AUC that you wanted.

Did you have enough data from the centers that provided the largest number of patients as to whether or not you need to make adjustments? Could you make any comments on whether or not you would normally recommend adjustments for the weight in those calculations?

DR. VAUGHAN: I think Dr. Reardan can give you the distribution of dose.

DR. REARDAN: We may have a slide on the distribution of weights in the trial, the dosing slide.

The protocol -- just a little background -- allowed the physicians the choice of dosing based on ideal body weight, actual body weight, or adjusted ideal body weight at the physician's choice. The majority of the patients in our trial were dosed based on ideal body weight.

[Slide.]

This shows roughly the numbers of patients in the

first column for ideal body weight, adjusted, ideal body weight, and actual body weight across the trial.

In terms of the center-specific effect, we have not examined that carefully just because of the numbers of patients.

You are probably referring to one of the kinetic slides that Dr. Vaughan showed.

DR. VAUGHAN: You were referring to the distribution of AUCs?

DR. PAPADOPOULOS: Right.

DR. VAUGHAN: There were three outliers in the first dose, and I can explain those, or I could also address the AUC influence on VOD.

Dr. Seng-Jaw Soong and I, who is Director of Biostatistics at UAB, did an analysis of VOD risk that you saw one or two slides from, and AUC was only a borderline contributor in univariate analysis, and dropped out in logistic regression.

So, with this tight distribution, we didn't see a major contribution of AUC to VOD risk. That is why it is easier to look at other factors. In earlier studies with the oral preparation, with the wide CDs, the effect of AUC just overwhelmed any other possible contributor.

DR. MILLER: The definition of VOD is a clinical definition based on either a triad or a quartet of clinical

signs and symptoms. I can't pull out the data on the patients who had elevated bilirubins before day 28, which is one of the first diagnostic criteria. The patients who had that, but were not called VOD, why they were not called VOD.

I think it would be helpful if we saw something that showed that weight wasn't -- because I mean it is clear that two of the criteria that could be used are not at all subjective, so I think that data would help us, because this was not a blinded trial, and I can't really see, there is not a lot of discussion about how it was chosen, what was or wasn't VOD.

Do you have that data on each of those patients who had bilirubins above 2, so we can more clearly see why they were not called VOD?

DR. REARDAN: Let me explain a little bit how we went about this. First of all, if a physician at the site identified a patient as having VOD, we accepted that determination.

When Dr. Vaughan went to do his multivariate analysis on VOD, we had the people at Lineberry Research program a database, and all patients with high bilirubin above a certain level were examined, and these were also addressed by Dr. Vaughan in an independent review, and I think he assessed 10 or 12 patients from which the table that you saw presented today was generated.

Dr. Vaughan, maybe you would like to comment on this.

DR. VAUGHAN: We started with the six patients who were identified by site investigators as having VOD. I believe two of those were biopsy proven, and they were pretty extensively worked up.

I did early on an independent review of all those records, of those six records, and only four met Jones criteria. I also looked at MacDonald criteria, but the Jones, the one I chose is most rigorous.

Two of them didn't. One of them had like a 6 or 7 percent weight gain on day +1 and 2, and an elevated bilirubin on day 20, and somewhere in between a note in the chart about some right upper quadrant pain.

So, I think the site investigators were pretty generous about the diagnosis of VOD. The database was then searched for all patients with greater than 5 percent weight gain and all patients with elevated bilirubin, and only two additional cases were identified who had both.

I looked at those two cases, and did not feel they met the criteria. So, an attempt was made to try to ferret out any missed VOD or underdiagnosed VOD.

DR. MILLER: Do you have that in a tabular form?

DR. VAUGHAN: I did at ASH, but I didn't bring those slides. Sorry.

DR. MILLER: Thank you. The second question. In the patients, do you have any data on the patients who had AUCs over 1500, that group, just taken out by itself, what the outcomes were on those patients?

Those are the patients that, in practice now, many places would adjust downwards, and I think we would like to know whether or not -- with that group of patients, over 1500 AUC, you would expect at least a 30 percent incidence of VOD or preparative regimen toxicity.

Do you have just those patients broken out? I know it was about 10 patients, that we can see what happened to those?

DR. VAUGHAN: Is there a slide on that?

DR. DUTCHER: You have to identify yourself and use the microphone, please.

DR. VAUGHAN: This is Ms. Shari Lennon from Orphan Medical, who assisted us and knows the data set very well.

MS. LENNON: Two of those patients did get VOD. One, it was a fatal case of VOD.

DR. MILLER: I see that, but what are the other outcomes on those 10 patients? High busulfan AUCs is not just a marker for VOD, but also mucositis, interstitial pneumonitides, and so the question is, is 1500 AUC important after I.V. as it is after oral administration?

I know VOD is one measure, but can you just tell

us what happened to those 10 patients?

MS. LENNON: If you can give me one minute, I will pull some data for you, and Dr. Vaughan can address it.

DR. VAUGHAN: I think it is a very, very good question. It's the first pass effect gets at that, and it gets at the issue of whether this variability is just measurement variability in the laboratory or sample time variability in the clinic as opposed to that much real difference. There are certainly other sources of that kind of standard deviation.

There were three outliers you saw. Those were clearly sampling errors, but we left in the data to be complete. There was blood drawn late again, as happened in one of the other cases. I don't see in the broad view any AUC correlation here, although one could do quartile analysis or something like that, I suppose.

DR. REARDAN: We did do an analysis looking at low AUC and relapse. We didn't see anything. I don't know if Derry is here and wants to comment, but we tried to look for a relationship to AUC and disease outcome, and the database was small. We didn't see any statistical. We were using simple T tests on AUCs versus disease outcome, primarily looking at low end, but we didn't pull anything out from that. I guess we don't have a table that you are asking for, I am sorry.

DR. MILLER: Another question about children. Busulfan, pharmacokinetics are very different in children after the oral administration, and busulfan is hardest to give to children. We often have to put NG tubes down to get into children.

I know you are doing a study now, but why were children not included earlier in this analysis, so that we could have the data potentially when we are making this evaluation in the group that may need it the most?

DR. REARDAN: We recognize your position, and actually FDA asked us very strongly at the January '97 meeting to initiate a study in pediatrics. That study was initiated over a year and a half ago in over 20 centers in the United States.

To date, we have entered 12 patients in that study. I think there are just not a lot of patients. You know, the pediatric population in the United States that is transplanted each year, that is eligible for busulfan, is in the range of 5- to 600 patients, and, of course, that is spread out across the country.

We recognize and are working with many pediatricians, and John Slattery up to Fred Hutch has published a lot of data on that, and we agree with you and we are pursuing that indication actively.

We hope to be supplementing this NDA as soon as

those studies are completed.

DR. SANTANA: As a corollary to that, since I am a pediatrician, I want to comment on that, your last two words on your indication are genetic diseases, and no data at all has been presented on pharmacokinetic variability in that patient population.

As you know, if you are talking about genetic diseases the way I think about them, you are talking about hematologic problems like sickle cell or metabolic storage diseases that are also seen in pediatrics, and those patients are truly different than the leukemia patients, too, in terms of their pharmacodynamics, so that I would encourage you to continue pediatric studies in specific populations, which may be very different than the leukemia or cancer populations if you truly want an indication for genetic diseases.

DR. REARDAN: Our protocol in pediatrics does include genetic diseases, and maybe Shari or Nancy can tell us. I mean of the 12 patients, I think 3 or 4 have been genetic disease patients, and that trial is open for children with genetic diseases.

DR. SANTANA: Thank you.

DR. DUTCHER: Dr. Sledge.

DR. SLEDGE: I appreciate the desire to have a broad indication in allo. It strikes me as a little bit

unusual that you would ask for an indication in breast cancer, ovarian cancer, given (a) the controversial nature of transplant at all in those diseases; and (b) the true rarity of trials that have looked at busulfan in either breast or ovarian cancer.

I would appreciate a comment.

DR. REARDAN: Well, I think we agree that data in breast cancer and ovarian cancer is weak. There are no controlled studies reported to date. I think the point, the original indication that we had proposed had been for patients who are selected by their physician to go into transplant, that busulfan should be available as an option for those patients.

We have reported some open-label data in patients with breast cancer. I agree with you the data is weaker in breast cancer, and I think that is not a question that the agency is going to be asking the panel today. I think FDA has made up their mind on breast cancer already.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Just a quick question to clarify some of the pharmacokinetic dosing issues. The comment has been made that it may be important to be able to individualize dose to achieve the target AUC, although my interpretation of the PK data that we have seen is that with the I.V. formulation, in fact, it probably won't be

necessary to do that, because, number one, it does not appear with this formulation that there is an identifiable relationship between AUC and risk of VOD, and that appears to be because, if I understood one of Dr. Vaughan's slides correctly, in 90 percent of the patients, the AUC was actually 1500 or less, so that, in fact, most of the patients with the recommended dose are below the threshold for VOD risk.

So, just to clarify, I mean although this formulation would facilitate individualized dosing, it is not actually clear that individualized dosing would be necessary with this formulation.

DR. REARDAN: I think I agree. Dr. Vaughan has got a perspective on limited dose sampling, and, Dr. Andersson, did you want to take this question?

DR. ANDERSSON: Yes. I would like to fill in that I agree with you at least based on the data we have now, we cannot say that we have any increased incidence of serious toxicities or any increased relapse frequency when we look at the different groups of patients.

Since I come from M.D. Anderson, the tradition there is to dose per ideal body weight, which would be the most conservative, normal or ideal, whichever is lower, so that very skinny patients will be dosed per their actual body weight.

When we compare it to some of the other centers, where it was used routinely dose adjustment with then a significantly higher dose given to overweight patients, we cannot see that we have any increased risk of serious complications or any increased relapse frequency in our patients.

Now, we have to be a little bit careful because the number of patients is still limited, and the overall follow-up is still unfortunately also somewhat limited, but at least based on the data we have, we are inclined to agree completely with you.

DR. DUTCHER: Dr. Albain.

DR. ALBAIN: You mentioned that the patients in your trials had either typical cyclosporin prophylaxis for GVH or tacrolimus.

Was there any evaluation of adverse events in interaction with the GVHD prophylaxis in the allo group?

DR. REARDAN: Dr. Andersson, can you take that? The question, as I understand it, is there any increased adverse event in the patient population, the allo group, who received GVHD prophylaxis with cyclosporin and FK-506.

DR. ANDERSSON: Are you thinking of any specific side effect, such as liver problems or lung problems or the HUS TTP, or are you thinking about just globally, side effects, period?

DR. ALBAIN: Well, the specific ones you mentioned.

DR. ANDERSSON: We have not been able to identify that overall. I could be somewhat facetious and say that it might be due to the low incidence overall of CIS toxicities. I wouldn't do that. I will be totally open with you and say that we have not looked at the question with the specific idea in mind whether it was cyclosporin or tacrolimus, however, my recollection is that M.D. Anderson was the only site that consistently used tacrolimus as standard of care where all the other sites used cyclosporin-based immunoprophylaxis, and we did look at relapse frequency.

We have an overhead that looks at relapse frequency just broken down per site, participating site, and there isn't really any difference, serious toxicities versus relapse frequency. If we look at M.D. Anderson versus the rest, it evens out, serious toxicities or deaths, it's about equal in relation to the number of patients entered, and if we look at relapse frequency overall, it's about the same.

DR. PAPADOPOULOS: Just as a follow-up to what you are discussing right now, since many of the patients were from M.D. Anderson, was the mini-methotrexate dosing used for these patients?

DR. ANDERSSON: Yes. The majority, at least in our patient cohort, we have used methotrexate 5 mg/M^2 day 1,

3, and 6, and then tacrolimus starting on day -2.

DR. PAPADOPOULOS: Do you think that that might be a reason why you had in the entire group, certainly since the majority of patients came from M.D. Anderson, less toxicity since methotrexate in association with at least oral busulfan has been thought to perhaps increase the incidence of VOD or the risk?

DR. ANDERSSON: How do you mean "less toxicity"? I would turn it around and say would you expect that we have more toxicity when we add an agent like methotrexate, and compared with if we had used just steroids, steroids and cyclosporin, which Peter Tutschka originally used.

I would say yes, and I would also like to tie it back to Dr. Miller's question before about patients with hyperbilirubinemia, because as you know, as a clinician, when you have taken care of a certain number of patients, you start recognizing certain patterns.

One of them is that in these patients, quite frequently you give the stem cells on day zero, you have a little blip in bilirubin on day 1. When you give the methotrexate, it comes down on day 2, you give methotrexate on day 3, you see the bilirubin is up to 2 1/2 on day 4, it's back down on day 6. When you give the next dose, you get a little blip again for one or two days, and then it comes right back down.

The transaminases did not budge. The patients weren't aware of it, the nurses weren't aware of it, it was simply just an artifact in the flow sheets, so to say, but after a while we start recognizing this, and just relate it to the methotrexate or possibly the methotrexate superimposed on top of the busulfan, which is what I suppose you are aiming at.

We were somewhat concerned in the first half dozen patients or so that based on the literature data and our own experience in the past, when we used slightly higher dose of methotrexate, like the Hutchinson group, the 10 mg/M, and with oral busulfan, we had become a little bit gun shy about that, so to say, but after the first few patients, now with our lower mini-dose schedule, we saw we got away with it, and we felt totally comfortable about using 5 mg/M, because we could not see by any long shot that we had any increased clinical toxicity from adding methotrexate.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: I have one other question about the PK. You are trying to make the case that there is less variability both within and between patients with the I.V. formulation, and the data that were shown to us, Dr. Vaughan showed us some absolute numbers, and said, well, you know, here, the standard deviation is 100, and that is less than 400, so, you know, there is less variability, but that is

not very informative.

What about the percent coefficient of variation between the oral and the I.V.? It struck me just sort of casually looking at the data that the percent CV for most of the PK parameters is about 20 percent for both oral and I.V. So, that would suggest that there is not a lot of difference in variability across the two preparations. Is that correct?

DR. REARDAN: I will just make a comment, and then I will turn this over to Dr. Vaughan.

We tried to address the specific patients with the spaghetti plots that you saw, and those did include all patients, and hopefully, visually, you can see the wide variation in oral and the tighter variation in the I.V.

If we want to look at the percent CVs, I mean, in general, the numbers for Tmax or AUC or Cmax are not that different between oral and I.V. In fact, FDA agrees and said they are equivalent, and so the CVs or standard deviations are lower for the parameters with the intravenous product. I don't think we have done the percent CV calculation, but I would expect they would be lower and tighter for the I.V., as well.

Dr. Vaughan.

DR. VAUGHAN: There are I think two points. One is that we chose to express all the data one way or the

other throughout the presentation, and we chose mean and standard deviation because all the previous literature for oral was in mean and standard deviation.

We do have the data on median and CV for all this. There is very little difference in the median, 20, 30, 40 units difference between the median and the mean for almost all of these, particularly for the I.V., and if you look at the scattergrams, it really does look bell shaped, so I think that mean and standard deviation really do define the population.

The comparison of two standard deviations, we discussed with the statisticians at some length. You really have an n of 1 when you have a standard deviation. I mean a mean has an n of all the patients in the trial. You have an n of 1 with the standard deviation. To compare the difference between two standard deviations requires either huge numbers of trials, each with their own standard deviation all designed the same, or some very large number to do some other method.

[Slide.]

Now, that is my understanding of the problem of comparing two standard deviations, so what we are left with is just looking at the data.

DR. SCHILSKY: This is helpful just to show us this. It does look like the percent CDs are a little bit

less for the I.V. formulation.

DR. VAUGHAN: Particularly for Tmax, and for limited sampling strategies, knowing where the Tmax is, is really important, and that is one of the things I tried to say when I said the Busulfex pharmacokinetics are superior, and superior in terms of our ability to understand them, and in answer to the AUC question why do pharmacokinetically directed therapy, well, you know, I think Victor answered that in terms of the half-life in children is shorter and variable, and the special populations, there are going to certainly be situations where it is necessary to do that.

DR. REARDAN: The other comment that I think you need to consider is that 2 out of 12 patients in the BUS-2 study, the Phase 1 study, vomited their oral dose, and their kinetics were unevaluable.

In two of the patients in the Amendment 4, we never reached Cmax. Their doses were still rising at the 6-hour point, so I think we have got the kinetic data and then there is a clinical endpoint on which we base our superiority claim.

DR. DUTCHER: Dr. Santana.

DR. SANTANA: To kind of follow up in that same discussion, so what are the recommendations for the sponsor in terms of monitoring and dose adjustments when you use the I.V. formulation? Then, I have a point of clarification

after that.

DR. REARDAN: We don't believe that limited sampling is necessary. Dr. Vaughan has pointed out that with the current oral product, it has become standard practice, and certainly in children, we are monitoring everyone because you can't always predict when the cutoff is about age 4, when a 4-year-old will have twice the clearance rate of a 5-year-old, and so for children, certainly monitoring is probably going to continue to be important certainly in the children under 4.

For adults, I think the Tmax is very reproducible. It occurs always at the end of the infusion. If a physician wanted to get comfortable and felt they needed to look at a population in their own center, they could look at Cmax and see how reproducible that is.

We believe that our AUC is predictable from dose 1 to dose 9 to dose 13, and that is the importance of having an intravenous product, that if you do decide to do kinetics, you know where you are going to go with the next dose.

I don't know if that answers your whole question. You said you had one more part.

DR. SANTANA: It is completely different, but getting back to that, I still don't understand what the recommendation is for doses adjustment. I mean you go down

by what percent? Is it individualized for every patient?

DR. REARDAN: The company has not recommended in our labeling that sampling or limited sampling is necessary for the use of this product.

DR. SANTANA: Okay. The other is just a point of clarification. I got the suspicion on one of your studies, I don't know whether it was the BUS-3 or the BUS-4, that the patients may have received a growth factor, either GM or G-CSF. Is that true, and if it is true, does that somehow influence the engraftment neutrophil data that you presented that makes it look so favorable compared to the historical?

DR. REARDAN: Again, in all of our studies, we allowed the centers to use their standard supportive care, and I think we may have a slide on that question. I will let Dr. Andersson answer that.

DR. ANDERSSON: The majority of patients have indeed received nupragen post-transplant until recovery, and then, if necessary, for low counts after recovery.

The reason that we in our, not comparison, but when I put up the slide showing the recovery data, after oral BuCy versus Busulfex plus cytoxan, side by side, we elected to only look at articles that had been published in about the last five years for this specific reason.

As you are implying, supportive care has changed quite dramatically, and we were concerned also that most of

the literature up until the early nineties, up until 1990, 1991, would be based on patients that were transplanted before there was open access to growth factors that could be used to support engraftment and recovery.

DR. DUTCHER: One last question.

DR. MILLER: You had a 26 percent incidence of Grade 3 and 4 stomatitis. Did you look at area under the curve correlation? I think I asked a slightly different question before, but do you actually have the AUC associated with stomatitis, because that will get past the question of a first pass metabolism, but that would get to your question of whether or not the high AUCs does affect regimen toxicity.

DR. REARDAN: Shari is shaking her head that I don't have that specific slide. I am sure we could pull that together, but I can't give you an answer today.

DR. ANDERSSON: We are aware of the connection that has also been published about mucositis as a predictor for VOD coming two weeks later or so. We have not yet gone through the database and correlated the pharmacokinetics on each individual patient to correlate with mucositis.

It is an interesting proposal because we had a higher incidence of mucositis than of VOD certainly, and here we might find a connection. As you may recall, we did not have any confirmation of VOD in our few patients with

VOD that it was well connected to the AUC of busulfan, which may have been due to the low number of patients developing VOD, but still there was no connection.

For mucositis, we have to say we don't know yet.

DR. DUTCHER: One more last question.

DR. MARGOLIN: Dr. Simon, if I can ask a question, just to probe a little further. If is really impossible, statistically impossible to compare two standard deviations? There seems to be a focus on the difference in variability, but we don't really know.

DR. SIMON: No, I disagree with the company's statement on that. I think if you have a standard deviation, it depends on -- you have two standard deviations, each one is based on a certain number of data points. The variance estimates divided by the true variance has a chi-square distribution.

Your null hypothesis is that those two true variances are the same, so you can do either test based just on those two standard deviations and the number of data points that goes into each of them. You don't need any other data.

DR. MARGOLIN: But you didn't actually do that, right?

DR. DUTCHER: Let's take a 15-minute break. We will be back at 10 o'clock.

[Recess.]

DR. DUTCHER: Let's go ahead with the FDA presentation. Dr. Griebel.

FDA Presentation

Donna Griebel, M.D.

DR. GRIEBEL: I am Donna Griebel. I will be summarizing the FDA's review of this application.

[Slide.]

There were a number of us who worked on this review, and I will actually be joined today briefly by Dr. Brian Booth from Biopharmaceutics, who will be discussing the pharmacokinetic issues in the application.

[Slide.]

In terms of the regulatory historical highlights, a number of these slides were already shown by the sponsor, so I will try to rush through them.

The meeting in January, we agreed upon the goals that needed to be met within the application. They included demonstrating the comparability of the bioavailability between the two formulations, having an adequate accrual to the Phase 2 trials to establish safety associated with the I.V. formulation.

[Slide.]

We chose the efficacy endpoints to be myeloablation and time to engraftment, and we agreed upon a

complete and comprehensive literature review that provided evidence of efficacy and safety for the oral formulation as preparative therapy in lieu of the same information for the intravenous formulation.

[Slide.]

It was agreed that the indication would be derived from the Phase 2 study data, as well as that literature review, and this was further clarified later that specific indications within the global bone marrow transplantation setting needed to be specified and data needed to be submitted to support each specific setting.

[Slide.]

Because of that, the proposed indication is very detailed and lengthy. We have for use in combination with other chemotherapeutic agents and/or radiotherapy for a long list of diseases that include ALL, AML, CML, non-Hodgkin's lymphoma, Hodgkin's disease, myeloma, myelodysplastic syndrome, breast cancer, ovarian cancer, and genetic diseases.

[Slide.]

The core studies for the intravenous formulation data were BUS-3 and BUS-4. You have already heard that BUS-3 was the autologous study, BUS-4 was the allogeneic study. Both allowed for optional use of prophylactic G-CSF.

[Slide.]

Moving on to the first issue that we agreed upon for goals is the pharmacokinetic issue, and Dr. Brian Booth will be joining me now.

Brian Booth, Ph.D.

DR. BOOTH: Good morning.

[Slide.]

With regard to the pharmacokinetic characterization of Busulfex, the sponsor essentially had to answer two questions. The first was to determine whether Busulfex has the same pharmacokinetic characteristics as oral busulfan, and secondly, the sponsor wanted to demonstrate that Busulfex is pharmacokinetically superior to oral busulfan based on the variability around the PK parameters.

[Slide.]

In order to address these questions, the sponsor chose to compare the pharmacokinetics of oral busulfan after the first dose to the steady-state pharmacokinetics of Busulfex after the 9th dose.

[Slide.]

In order to make this comparison, the area under the Posner concentration curve after the first dose has to be turned from zero to infinity, and this should equal the area under the curve of the Busulfex at steady-state during the dosing interval of zero to 6 hours.

This particular measurement can be made accurately and easily from the data that is obtained from the patient, however, in this case, it isn't possible to observe the disposition of a drug for an infinite period of time, and this necessitates that a certain portion of the AUC be estimated.

The FDA recommends that for long-acting drugs, this disposition should be observed for three half-lives, and this allows a terminal estimate of about 12 percent of the total AUC to be made.

For shorter acting drugs, such as busulfan, the FDA recommends that disposition should be observed for five half-lives, and this allows a much smaller percentage of the AUC to be estimated.

In the studies reported here by the sponsor, both oral busulfan and Busulfex are observed for a period of two half-lives, and as a consequence, a much larger portion of the AUC had to be estimated in these studies.

[Slide.]

Across the studies that were submitted by the sponsor, the dose 1 estimates of AUC ranged from 30 to 40 percent, and the ranges in the study are listed here on the left. Overall, the average estimate of dose 1 AUC was 35 percent, and this is unacceptably high as it incorporates too much error in this measurement.

[Slide.]

As a consequence, the FDA discounted the comparison of the oral busulfan AUC after dose 1 to that of the AUC of Busulfex at dose 9, and furthermore, any pharmacokinetic parameters derived from the AUC cannot be compared between these two periods for the same reason.

[Slide.]

In order to answer these questions, the FDA conducted an independent analysis in which the AUC of oral busulfan after the first dose was compared to the AUC of intravenous Busulfex after the first dose in other studies.

In this case, only observed data was used, and no terminal estimations of the AUCs are made.

Now, this approach is also limited in a couple respects. Only 9 patients received oral busulfan compared to approximately 100 who received Busulfex, and the comparisons that were made are made across studies as opposed to within studies.

[Slide.]

Nevertheless, we observed that following oral administration of busulfan, the AUC was about 790 micromolar per minute, and this is apparently similar to the AUCs that were attained following intravenous administration of Busulfex.

The variability, as reflected by the coefficients

of variation, were also quite low and conserved across the studies despite the different routes of administration.

In the last column here, I have included the data submitted by the sponsor in the NDA, and you can see that their values correspond quite closely with those of the FDA's.

[Slide.]

Based on this analysis, the FDA has concluded that Busulfex and oral busulfan have the same pharmacokinetic characteristics, and the variability around these pharmacokinetic characteristics are the same for Busulfex and oral busulfan.

Thank you.

Donna Griebel, M.D.

DR. GRIEBEL: Briefly, before I go into the clinical studies, I wanted to touch on the toxicity of the solvent in Busulfex. It's dimethylacetamide.

[Slide.]

This solvent has not previously been approved as an inactive ingredient before this application. Repeated dosing studies have been reported to cause hepatic injuries, injury in animals and humans. The human data is based on a Phase 1 trial from the sixties when this agent was actually examined as a chemotherapeutic agent.

At higher doses than delivered in a conditioning

regimen with Busulfex, patients did have elevation of transaminases which resolved with stopping the DMA. Similarly, high doses have been reported to cause neurologic symptoms in humans. When you review the same study, the same Phase 1 trial, the neurologic symptoms were confusion, lethargy, and hallucinations.

I did a relative dose calculation comparing it to what patients normally would receive with conditioning regimen with Busulfex, and the first patient who demonstrated hallucinations was in a patient who received one and a half times the dose that would be anticipated to be given in a conditioning regimen, and the next jump was to two times the dose that would normally be expected to be received.

These hallucinations resolved. They were, interestingly, generally delayed by about 24 hours after the last dose of the DMA, and DMA causes unusually vascular malformations in fetal mice.

[Slide.]

Moving on to the comparative efficacy and safety between the intravenous and oral formulations, BUS-3 was an autologous study, and we have already heard that it was more heavily weighed toward patients with non-Hodgkin's lymphoma and Hodgkin's disease, and these patients had a history of heavy pretreatment.

[Slide.]

The efficacy endpoint definitions between the two trials were the same. Myeloablation was dropping the ANC below 500 or the ALC below 100 or platelet count less than 20,000 or developing bleeding that required transfusion.

Engraftment was reaching an ANC greater than 500.

[Slide.]

Nonengraftment was not reaching an ANC greater than 500 within 100 days of transplant, and late graft failure was going over 500 and then dropping back down below within the first 100 days.

[Slide.]

In terms of efficacy on BUS-3, myeloablation was achieved in 100 percent of the patients, engraftment in 100 percent of the patients. The median time to engraftment, we have heard was 10 days.

On my review of the serial CBCs, I changed some of the engraftment days, but this had low impact on the median time to engraftment and changed it only to 10.5 days, there were no late graft failures.

[Slide.]

To compare this to oral busulfan efficacy, I went to the literature and I wanted to use randomized controlled trials. Autologous randomized controlled trials using busulfan, I ended up with an autologous transplantation

group of articles for patients with AML and for CR, so we have a difference already between these two patient populations as BUS-3 was more heavily weighed towards lymphomas.

The doses here were higher for cytoxan, 200 mg/kg versus 120 mg/kg, and there was no prophylactic use of G-CSF in the literature, whereas, in BUS-3, all but three patients were treated with prophylactic G-CSF.

Nevertheless, with those caveats in mind, the median time to ANC of greater than 500 was 10 1/2 days versus 25 to 32 days in the literature, no graft failure versus very low graft failure.

[Slide.]

In terms of the comparable safety, using the same literature that I have described, VOD 2 percent versus 2.3 to 6.1 percent, that 6.1 percent is in parentheses because that article reported it as deaths from VOD, they did not report the absolute number of patients who developed VOD in that study, and that was probably higher.

I did not find reports of pulmonary events in the autologous articles. It was 2 percent in this study. No deaths within the first 100 days versus in this AML population for CR, 6.5 to 15 percent, and hemorrhagic cystitis, one patient.

[Slide.]

We have already heard about the one patient who developed a seizure two days after the last dose of busulfan, and they were on prophylactic dilantin.

[Slide.]

BUS-4, a patient as old as 63 was treated with allogeneic transplantation in this study. They were heavily pretreated, eight had undergone prior transplantation.

[Slide.]

One hundred percent myeloablation, 100 percent engraftment. That asterisk refers to the fact that there was one evaluable patient that was not counted here. That patient did not engraft before they died. Their death occurred seven days after the median time for engraftment observed in this study, which was 13 days, but within the range that was seen for engraftment in the study for the overall study population, and there was no late graft failure.

[Slide.]

Again, comparing to the literature for the oral busulfan data, this time different literature, but again randomized controlled trials, this is a mixed population of hematologic malignancies, no G-CSF used prophylactically, and it was used prophylactically in this study in all but 13 patients.

Thirteen days median time to engraftment versus 19

to 20 days. No graft failure versus 2.3 to 6.1 percent graft failure.

[Slide.]

Comparing the safety, VOD, 8.2 percent versus 5.9 to 12 percent reported in the literature. Pulmonary events, this is a number derived by me. The literature focuses on interstitial pneumonitis, and I went through and looked at the pulmonary events, and if there was not documented infectious etiology, I tabulated it as a pulmonary event to try to make it more comparable to the literature, and came up with 8.2 percent versus 3.9 to 16.9 percent.

This is overall GVHD, all grades, 18 percent, higher in the literature, in the literature reported as greater than or equal to Grade 2, acute 26 to 41 percent, and 45 percent chronic, and hemorrhagic cystitis was comparable, 7 percent versus 11 to 24 percent.

[Slide.]

When looking at deaths reported within the first 100 days, in the literature, 4.1 to 21 percent, 13 percent in the study. There were two articles that reported non-leukemia related mortality, 28 percent in one article, a Kaplan-Meier probability of 27 percent in another.

I went through a looked at the death in the narratives associated. If there was no disease relapse associated at the time of death, I tabulated that patient,

and came up with 11 patients or 18 percent.

[Slide.]

So, a quick summary of the comparative efficacy conclusions. In terms of myeloablation the time to engraftment, the I.V. and oral formulations appeared comparable, as did the safety between the two formulations.

[Slide.]

Moving on to the literature review, as the sponsor already noted, this was a large part of this application. As you noted, in over 2,000 articles recovered with the literature search, there were potentially a lot of articles to process.

I chose to focus on randomized control trials to help focus the review. In evidence-based medicine review articles, this type of data is referred to as Level I evidence, and you will see me refer to it as such in subsequent slides.

When I looked at these trials, I was guided by the proposed indication. I looked to see which diseases were being treated in the trials, what sort of stem cell transplantation was being used, and what was the busulfan combined with, what drugs, what doses, was it combined with radiation therapy.

[Slide.]

Here is the summary slide of the Level I studies

recovered by the sponsor and by me. In terms of allotransplantation for AML, there were three Level I studies in which 106 patients were treated with busulfan; autologous transplantation for AML, four Level I studies, 356 patients treated with busulfan.

Four Level I studies for CML, they were allogeneic transplant studies, 188 patients treated with busulfan. Two of the Level I studies accrued patients with ALL. That came to 41 patients treated with busulfan. One of the studies allowed patients with lymphoma to participate in the trial. They did not specify whether they had non-Hodgkin's lymphoma or Hodgkin's disease. Three were treated with busulfan.

[Slide.]

I will start working through these different indications. Starting with AML allogeneic transplantation, here are the three papers which provided Level I evidence in this indication.

This was a French study. This was a SWOG study. This is a Nordic BMT study. Only one of these studies limited their population to patients with AML. The remaining two studies had a mixed hematologic malignancy population that included AML, ALL, and CML. This Nordic BMT study brings in the four lymphoma patients that I mentioned earlier.

Not only was the study limited to patients with

AML, but it was limited to patients who were in first CR. These studies that were mixed hematologic malignancies, the Ringden study had patients both in first CR versus patients beyond first CR, and the SWOG study actually targeted a patient population that was beyond first CR.

All of the studies combined busulfan with cytoxan, 120 mg/kg, all compared to a TBI arm. The SWOG study was unique in that the TBI was combined with etoposide.

[Slide.]

This schematic is going to come up over and over again, and I will quickly explain it. If there is a face associated with an endpoint, that means that article did a formal statistical analysis of that endpoint. If the face is unhappy in the analysis, the busulfan arm came out statistically significantly inferior. If the face is noncommittal, neither arm came out as significantly superior.

As you can see, the three studies reported their endpoints in different time frames. If the Kaplan-Meier two-year relative risk analysis and the Kaplan-Meier three-year, this is the study limiting disease to AML, these are the mixed hematologic malignancy studies.

As you can see, the study that limits its patient population to patients with AML only, appears overwhelmingly bad for busulfan - inferior overall survival, inferior

disease-free survival, inferior relapse, treatment-related mortality was not found to be significantly different between arms.

The SWOG study found on a relative risk analysis in a mixed population of malignancies higher risk disease, that there was no significant difference between treatment arms.

[Slide.]

The Nordic study did find inferiority for the entire population. This study will come up over and over again in terms of disease-free survival, because for that particular endpoint, they did a subset analysis of each hematologic malignancy that was represented in the trial.

This study came out inferior, as well, in terms of treatment-related mortality and various toxicities.

[Slide.]

Moving on to the actual numbers, it has already been mentioned that this study has been criticized in the literature because of the unusually good results on the TBI arm, 75 percent overall survival, above 70 in disease-free survival, relapse 34 percent versus 14 percent.

Treatment related mortality was not found. It was 27 percent versus 8 percent, but it wasn't statistically significant. VOD was not formally analyzed. There were more cases on the busulfan arm, and engraftment occurred at

about the same time, 19 days.

[Slide.]

This is the SWOG study. Here is the mortality relative risk analysis 0.97 with this confidence interval, more deaths on the busulfan arm from VOD.

[Slide.]

This is the Nordic BMT study, mixed hematologic malignancies. Interestingly, this has the same overall survival that was criticized in the French study, 76 percent.

Here is the subset analysis of the AML subset. 61 percent versus 64 percent, p was 0.37. There was a greater representation on the busulfan arm in this study of patients who were beyond first CR. No difference in relapse. Treatment related mortality, the numbers are very similar to the French study, 28 percent versus 9 percent. The p value was significant.

[Slide.]

This study is relatively bleak in terms of toxicity analyses. VOD was significantly worse, hemorrhagic cystitis was significantly worse, as were seizures for the busulfan arm. The patients engrafted in the same time frame, 20 days.

[Slide.]

So, revisiting the schematic, have two of three

Level I trials that appear to argue against an indication in this setting - AML, allogeneic, BMT.

It appeared when I reviewed the literature that although BMT is commonly used in AML, there is still some controversy associated with it, particularly in the timing of the BMT.

There are patients who are cured with induction chemotherapy, particularly when combined with intensive dose consolidation post-induction therapy, so you have the potential if you take all comers to an allogeneic transplant of exposing people who are already cured to a significantly morbid treatment.

There was recently published in the New England Journal in December actually a comparison reported by Cassileth of a randomized control study in which the autologous arm was randomized versus the HDAC arm, but there was also an allogeneic transplantation arm in that study, and overall survival was significantly better on the HDAC arm as compared to the allogeneic BMT arm.

I went back and looked at these studies again from that standpoint. This is an AML and first CR study. What if you consider AML beyond first CR when it may be more valid to transplant these patients, and these, of course, were studies where those patients were included in the study, and they were targeted in this study.

In the SWOG study, they compared the outcome of patients who were in CR2 versus CR3, and found no significant difference in outcome and overall survival and disease-free survival between those groups and the treatment arms.

In the Ringden study, when they looked at that analysis of the patients who were beyond first CR, they found that it carried through, that busulfan continued to be an inferior conditioning regimen.

So, taking the schematic at face value, there does not appear to be a strong recommendation for an indication in this setting.

[Slide.]

Well, this is autologous transplantation data. There is actually four studies. There is a tagalong trial that is on a following slide. It is a pediatric trial.

These three are adult studies. All of them, including the pediatric trial, focused on patients with AML and first CR. They all used a cytoxan dose that was higher than what we saw in the allogeneic setting, 200 mg/kg.

The structure of these studies is the same. There was a randomization between autologous transplantation with busulfan conditioning regimen versus some sort of intensive consolidation chemotherapy post-induction therapy. This specific study was unique in that the busulfan was combined

with melphalan, and this study and the pediatric study used purged marrow.

[Slide.]

Here is the schematic again. I threw in a little bit of a twist with the arrows. That is because the numbers were given for comparison in these endpoints, but there was no formal statistical analysis performed on them, but the trends carried across the trials, so I went ahead and included them.

In terms of relapse, autologous transplantation seems to do better than post-induction chemotherapy, but in terms of treatment-related mortality, autologous transplantation does worse, and, in fact, in the pediatric study it was found to be statistically significantly worse.

In terms of the survival outcome, autologous transplantation does not come out superior to post-induction chemotherapy, and, in fact, in this Cassileth study that was just published, it was inferior, significantly inferior to HDAC chemotherapy.

[Slide.]

That study is summarized here. Here is HDAC, 52 percent versus BuCy. This is autologous transplant, 43 percent, P 0.05, and as already mentioned, the allo comparison to the high-dose chemotherapy or high-dose Ara-C, the p was 0.04.

Here are the trends that we will see over and over again, more relapse with high-dose Ara-C, but lower treatment-related mortality.

[Slide.]

That is just the same message, lower relapse with autologous transplantation, but higher treatment-related mortality.

[Slide.]

The same message on this slide.

[Slide.]

Here is the pediatric trial where treatment-related mortality was 15 percent versus almost 3 percent, and it was significantly different.

[Slide.]

Given the fact that there did not appear to be superiority for the autologous transplantation compared to post-induction chemotherapy, and actual significant inferiority in this study, and inferiority in the treatment-related mortality in this study, we did not feel that it was strong evidence for an indication in this setting.

[Slide.]

Moving on to CML allogeneic transplantation, there are four studies, but luckily, you have seen two of them before, the mixed hematologic malignancies, the Nordic BMT study and the SWOG study, which will tag along on the next

slide.

Here are the two new ones. They are limited to CML, and they are limited to CML and chronic phase. All of these studies combined busulfan, the cytoxan 120 mg/M^2. All compare it to a TBI arm combined with cytoxan except for the SWOG study in which it was combined with etoposide.

[Slide.]

There is the schematic. We have different time frames of reporting - three years, five years, three years relative risk analysis. This is the SWOG study, Nordic study, and the two pure CML chronic phase studies.

Since we have seen these before, I am just going to revisit them first.

The Ringden study, we know for the overall subset was inferior for overall survival and toxicities. The CML subset analysis, there was no significant difference in disease-free survival. The numbers on each arm in the study were 30 and 27.

Perhaps the most meaningful studies in this setting are those that limit their disease to CML and the Clift and Devergie study. As you can see, there is not a lot of evidence that one arm is better than the other with all these uncommitted faces, although in this endpoint relapse, although in this endpoint relapse, the relative risk analysis, multivariate analysis found that relapse was

higher on busulfan.

[Slide.]

Just visiting the numbers, this is one of the CML-only studies. You can see the overlap and similar times to engraftment.

[Slide.]

The Devergie study, here is that relative risk of relapse 4.10, the confidence interval was 1 to 20, p 0.04.

These was a similar incidence of VOD on both arms. There were more cases that were fatal on the busulfan arm, but there was no formal analysis of this.

[Slide.]

We have discussed the SWOG study. There were more deaths from VOD.

[Slide.]

Here is the Ringden study again, and here is the subset analysis. You will notice that this number is lower. This is the busulfan arm, 67 percent disease-free survival versus 83 percent. The numbers were small, however, and the p value was not significant.

When I went back and looked at the study, there was a greater representation of patients in accelerated phase on this study in the busulfan arm.

[Slide.]

Here are these toxicities. Treatment-related

mortality, VOD, seizures, hemorrhagic cystitis, the same time to engraftment.

[Slide.]

Revisiting the schematic briefly, we felt that the most meaningful studies were these studies that were limited to CML.

[Slide.]

There was no statistically significant superiority for either arm in these two trials except for the multivariate analysis of relative risk in the French study. The two studies with the mixed hematologic malignancies, we saw that the Ringden study demonstrated inferiority in terms of overall survival for the entire population and in terms of toxicity.

[Slide.]

Looking for a little support for the similarity issue, I looked for reports of the bone marrow transplant registry, International Bone Marrow Transplant Registry. This is two-year leukemia-free survival, of course, not randomized data, and you see similarities between outcomes.

This similarity, of course, raises the issues of equivalence. These studies were not designed to be equivalent studies, the populations were not large enough. Trying to do an exploratory analysis, we thought about combining the populations of these two articles and trying

to increase the power to determine equivalence, but their endpoints were reported in different time frames, and that made that impossible.

[Slide.]

The biostatistician had an idea that we explored, which was to calculate the confidence interval for the observed differences in the probabilities of survival associated with each treatment arm of the study, and then use that confidence interval to get a gestalt about how meaningful an assumption of similarity was between the two treatment regimens.

[Slide.]

When we did that, this is the Clift study, subtracting the TBI arm from the busulfan arm, three-year event-free survival, worst case scenario for the busulfan arm was to be an absolute 12 percent inferior.

Worst case scenario for busulfan and three-year overall survival, absolute number of 13 percent. The French study, five-year disease-free survival, worst case scenario 23 percent inferior, and finally, overall survival in that study, only 10 percent inferiority as the worst case scenario.

These numbers in particular did not seem to challenge us or raise big issues of concern regarding making a conclusion of similarity between the two treatment arms

from these studies.

[Slide.]

Well, if you are going to say it is similar to CY/TBI, the CY/TBI work, it is a completely meaningless analysis or a conclusion if CY/TBI is completely inactive. In order to decide if CY/TBI has an effective conditioning regimen as CML, you end up doing some deductive reasoning.

[Slide.]

CY/TBI is historically the conditioning regimen that has been used. It was first developed. It becomes the most commonly used regimen that is used for CML, and actually review articles where I found this addressed said CY/TBI was the most common conditioning regimen along with busulfan and cytoxan.

So, when textbooks say that allogeneic BMT is the only curative therapy for CML, and this is listed as one of the most commonly used regimens for this treatment modality, it follows that it is an effective regimen.

Delving into this issue of BMT's efficacy in this disease, the decision tree for transplantation in CML is complicated. It is based on age, donor availability, of course, desire for curative therapy, and issues such as whether the patient is still in chronic phase.

[Slide.]

I looked for a randomized control trial comparing

allogeneic transplantation and CML versus using something like hydroxyurea, interferon, and I could not find one. There is a retrospective historical control study by Gale where he compared the IBMTR data for CML transplantation to a treatment arm or treatment in the study conducted by a German CML group, and what was found was early on after transplantation, there is actually significant survival disadvantage for transplantation. However, as you follow patients out, the curves cross, and ultimately, there is a significant survival advantage for being transplantation.

[Slide.]

I am almost running out of water, so I need to be winding down. ALL, luckily, here are those studies haunting us again because they included a mixed malignancy population. ALL, 48 patients in this study, 38 in this study. All together there were 41 that were treated with busulfan. Again, different degrees of risk, early CR, CR1 versus beyond first CR in the SWOG study.

[Slide.]

We have seen this schematic before. The ALL subset analysis in the Ringden study for disease-free survival was based on a small number of patients, 18 versus 20. It was not found to be statistically significant. The overall survival for the group, however, was inferior.

Given the fact that there were so few patients to

look at, only 41 treated with busulfan, and that this trial was overwhelmingly negative for the entire patient group, we were not comfortable with an indication in ALL allogeneic BMT.

[Slide.]

Speaking of low numbers, there were those four patients included in a Ringden Nordic BMT study, three of which were treated with busulfan. That did not appear to be enough patients to justify an indication or analysis in lymphoma, and, in fact, when I went back and looked at the uncontrolled trials, busulfan conditioning regimens did not appear to be commonly used at least yet in this disease.

[Slide.]

For the remaining diseases in the indication, I found no Level I evidence.

[Slide.]

A quick summary. AML allogeneic transplantation, three Level I studies, 106 patients treated with busulfan. We did not feel that the evidence was persuasive for an indication in this setting.

Autologous transplantation, four Level I studies, 356 patients. The autologous transplantation setting did not appear to have evidence to support it.

CML, four studies, 188 patients. We felt in particular if you focused on the trials that were limited to

CML in chronic phase, there was a potential for an indication in this area.

ALL, only 41 patients. One of the studies was overwhelmingly negative for a mixed group of patients treated in the trial, and we did not feel this was supportive.

Finally, the lymphoma patients, we did not feel that few number supported this indication either.

[Slide.]

All of the zeros, we said were not supportive.

[Slide.]

A quick summary. Is the pharmacokinetic profile similar between the two formulations? It appears to be so.

Are the efficacy endpoints, myeloablation and engraftment, comparable between the formulations? It appeared so, as did the safety.

[Slide.]

Does the literature establish that high-dose oral busulfan is a safe and efficacious component of conditioning for stem cell transplantation? If so, which diseases in what settings? We felt the best support was in the CML chronic phase with busulfan combined with cytoxan 120 mg/kg.

DR. DUTCHER: Thank you for a very succinct summary of a lot of data.

Questions for FDA?

Dr. Schilsky.

Questions from the Committee

DR. SCHILSKY: That was a terrific summary. It must have been an extraordinary amount of work.

I just have two questions. At the very beginning of your presentation, you talked about the dimethylacetamide solvent and the fact that it's not approved for use I guess with any drug, and then you just sort of left us hanging without any specific recommendation about whether the FDA actually has concerns about the use of DMA as a solvent for this preparation.

Could you comment further on that?

DR. GRIEBEL: This has been brought up over and over again apparently with this application from its early history. I just came in on the history late, around September of '98.

We would be much happier with a different solvent. When I hurriedly went over the Phase 1 trial to see the comparable doses, it was just hallucinations, it was confusion, they resolved, and it was at a higher dose than what is being used here.

I went back through the patient data that I had from this study looking for that, thinking maybe I would see lots of cases of it. There was the delirious patient that went for seven days. When I went back through the

medications, as is the case in transplantation, patients are on lots of drugs that have lots of side effects.

That particular patient, if I recall correctly, was on scheduled doses of compazine. There was decadron for the cytoxan. It is very difficult to sort out whether this is actually meaningful.

I found a couple -- well, two to four cases of confusion that had a timing similar to what was reported in the Phase 1 trial one day after busulfan, but that was the timing of giving decadron for cytoxan in the study, and I couldn't make sense of it.

DR. SCHILSKY: Just I guess so we understand, if Busulfex is approved, does that constitute, then, approval for use of DMA as a solvent or future intravenous medications?

DR. GRIEBEL: I am not sure I am the best regulatory person. I assume that that is what it implies.

DR. TEMPLE: It would go case by case. I mean there may be a greater need to use something like that here than elsewhere. You wouldn't want to do it if you didn't need to.

DR. SCHILSKY: I just wanted to understand the issue. Just one other question very briefly.

In all of the studies that you presented, I didn't see any study in which busulfan was combined with

radiotherapy, so I take it that your position would be that that is not an appropriate part of the proposed indication.

DR. GRIEBEL: That is my conclusion.

DR. DUTCHER: Dr. Miller.

DR. MILLER: Bone marrow transplant is a therapeutic modality, and a preparative regimen is part of the totality of that modality, and it is very difficult to tease out part from the transplant that there are not big randomized trials of any preparative regimen.

I that, at least looking at the initial discussion, the idea of a literature review was to support, and not actually requiring Type 1 data. There is a huge literature with busulfan regimen.

Busulfan was first used as a preparative regimen at Hopkins because we were set up -- before my time -- but at the cancer center across the city, and Dr. Santos was concerned about being able to get his patients over to TBI during the snowy season in Baltimore, so a non-TBI-containing regimen was initiated, and it has been used in huge numbers of transplants since then, many of which again were not randomized trials, but there is a huge data, and it's a type database that may not be in randomized trials.

So, I think from a transplant standpoint, you have to remember that not everybody can get TBI for reasons of either having radiation therapy before access to radiation

therapy, variability in radiation therapy, scheduling, et cetera, et cetera, and the expertise to give TBI is much more difficult than the expertise of figuring out how to give busulfan. So, there is a lot of reasons for non-TBI containing regimens.

One of the largest regimens outside of TBI is busulfan-containing regimens. So, that is sort of a plea for or a discussion of how, from a transplanter standpoint, the importance of busulfan in our armamentarium as a transplanter.

Second, when you look at the autologous transplant data, and you are comparing it to chemotherapy, again, you are not looking at busulfan, you are looking at the transplant, and what is not included in that survival advantage -- and it is written in when you are looking at it -- is the ability, the reason the transplant is not better is because the ability to salvage patients in second remission with transplant, many of which would contain busulfan-containing regimens, and that is written in the discussion, but not in the randomized trial.

Disease-free survival is better with transplant, however, survival is not better because you have to weigh transplanting patients who may be cured versus the ability to salvage those patients in second remission.

So, I think that is comparing apples and oranges

when you are looking at what a preparative regimen can do. There is data in lymphoma patients, particularly Hodgkin's disease, there is at least four studies that I know of in patients comparing, not randomized, but patients who got TBI versus those who could not get TBI, and so they were, because of previous mantle irradiation, comparing non-TBI with a busulfan-containing regimen, again, not randomized, but showing equivalency.

I think it is hard to say that busulfan is not an accepted standard of care when if you look at the last IBMTR, over 20 percent of the transplants in the United States are using it.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I don't want to turn this into a discussion that doesn't relate to the issues, but maybe this does. I really thought Dr. Griebel did a very nice job for one of the rare occasions that I have seen -- not of her doing a nice job --

[Laughter.]

DR. RAGHAVAN: Wait, there is no comma in there -- but did a very nice job of actually trying to bring reason to the whole transplant debate, and I think that it has always troubled me that so much of the transplant literature is predicated on the urgency of treating leukemics, which I recognize, but I am not sure that that actually excuses that

discipline from providing the same quality of evidence as provided in other disciplines.

So, I don't personally accept that just because it snows in Maryland at certain times of the year that that is a reason to have a lesser level of evidence required to prove points.

So, I think it is very refreshing to have heard the FDA analysis where they actually look at the trials that were tough to do, with large amounts of data, where at the end of the day, you have Level I evidence-based information. The fact that there are tons and tons of Phase 2 trials that are noncomparable because of selection bias doesn't really help us with the issue of trying to figure it out.

It might well be that Dr. Griebel has uncovered the fact that there has been a systematic error for the last decade where people, for convenience, have moved away from TBI because medical oncologists don't give TBI, and have actually introduced into the system a systematic reduction in outcome.

So, I don't know if that is the case, but I don't think that just saying, well, most of the evidence is Level II or III, therefore, we have to accept it as necessarily a good paradigm for this committee.

DR. DUTCHER: Dr. Papadopoulos.

DR. PAPADOPOULOS: A question about the review.

As extensive as it was, were you able to look at the pharmacokinetics, if there were any, of many of these trials using busulfan?

DR. GRIEBEL: Actually, the only pharmacokinetic data that I went back and looked at were actually pharmacokinetic studies from Hopkins and that have been referenced already by the sponsor.

Actually, that was one of my questions after hearing the presentation this morning. My conclusion from looking at that data, it wasn't standard of care to follow levels, and it appears that that is a wrong conclusion on my part.

DR. PAPADOPOULOS: Well, I think that the problem is several of these studies are I wouldn't say old, but they are not done within the last few years. Pharmacokinetics was not readily available during many of these studies.

Relapse was not the major problem between busulfan, cytoxan, and TBI cytoxan-containing regimens. It appeared mostly to be regimen-related toxicity, and I would argue that there is room for speculation that perhaps had pharmacokinetics been available during this time period and used for dose adjustments, the regimen-related toxicity would not necessarily have been greater, and just raises a question as to the validity of these comparisons in these older trials.

DR. DUTCHER: Dr. Simon.

DR. SIMON: Do you recall what Bob Gale's comparison of the CML registry data to the German group's data showed in terms of what the size of the effect was on long-term survival?

DR. GRIEBEL: No, I don't remember offhand, sorry.

DR. MILLER: If you look at the data for interferon, the best data is a 10 to 15 percent disease-free survival long term without transplant. Now, I don't remember the data, but when you get long term out, there is clearly a crossing of the curves, and the majority, especially in patients who are not interferon complete responders, bone marrow transplant is the only potential cure of those patients. In most studies, at least the 40 to 50 percent long-term disease-free survival. So, you know, there is no question about the curative potential of transplant.

DR. SIMON: It would be zero in the other group?

DR. MILLER: Interferon complete responders of which 10 to 15 percent of patients who get interferon are complete responders cytogenetically at a median of one year. In those patients, 85 percent of them are alive at 14 years, so cytogenetic complete responders.

However, in the 85 percent of patients who fail interferon, the median survival is between 4 and 6 years

with a tail, which probably goes down to zero.

DR. SIMON: As I understand it, that is not what Gale did. He wasn't just looking at those who first got interferon and failed it. He was looking at the interferon regimen, a series who got the interferon regimen including complete responders and non-complete responders to those who got the BuCy.

DR. MILLER: True, and so that includes the group of patients, and where there is a tail on that curve, but it is significantly inferior to the IBMTR transplant where the data would be -- I have a slide -- 40 to 50 percent in long-term disease-free survival at 10 years.

DR. SIMON: So, it would be like 40 to 50 percent versus 15 percent?

DR. MILLER: I don't remember the exact data, but if you look at all patients who were treated with interferon and hydrea it's low, 10-year survival.

DR. DUTCHER: Are there any ongoing studies using pharmacokinetic modeling comparing the CY/TBI and the BuCy right now to try to look at the issue of toxicity? Bill.

DR. VAUGHAN: There is one study in pediatrics called the Philadelphia Study, which compares BuCy and Cy/TBI, I think, and does call for pharmacokinetic analysis, and interestingly, targets AUC at 900 under dosing I would say intentionally to avoid the risk knowing the inaccuracy

of the test dose pharmacokinetics with the oral prep.

That study was temporarily suspended a few months ago because it looked like one arm might be significantly different from the other, but has been reopened, so apparently no result has been achieved yet.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: The vast majority of I believe transplants now for CML, or at least we are heading that way, are going to be unrelated donor transplants, and the question I have is about what we know about the adequacy of immunosuppression induced by busulfan and its comparability to TBI.

We have a little bit of the hematopoietic chimers and data, but not much. So, if the indication is going to be for CML, how is that going to be connected to the type of transplant?

DR. GRIEBEL: Well, I didn't extend it beyond the unrelated donors. I focused on what I had the data on, which was HLA-matched related, so I don't know the answer to that.

DR. MILLER: There is data using non-TBI-containing regimens in unrelated transplant. Dr. Henslee Downey has a non-TBI-containing regimen for her mismatched allogeneics using thiotepa, busulfan, and something else, I don't remember which, showing that you can get engraftment

at least with unrelated transplant.

Dr. Copelan also did a review, I think the same review you might have referenced, looking at the compilation of data, busulfan-containing regimens in mismatched unrelated transplants, again showing that you are able to get adequate engraftment and immunosuppression with busulfan. There have not been randomized trials, but there is data.

DR. DUTCHER: Other comments, discussion?

[No response.]

DR. DUTCHER: Thank you very much.

Committee Discussion and Vote

DR. DUTCHER: We should take a look at the questions that have been proposed.

This NDA has three principal components:

I. Two Phase 2 clinical trials that assess myeloablation, engraftment, and safety associated with Busulfex/cyclophosphamide conditioning regimen for stem cell transplantation, autologous 42 patients, allogeneic 62 patients.

II. Clinical studies to assess the Busulfex Injection pharmacokinetic profile relative to oral busulfan.

III. Literature review to determine the diseases where there is substantial evidence of the safety and efficacy of stem cell transplantation using an oral

busulfan-containing chemotherapy regimen.

We have some tables looking at engraftment efficacy in the autologous and in the allogeneic setting, and the summary of comparative safety looking at I.V. versus the literature for oral.

On the next page there are two more tables, and then the questions.

1. Do the Phase 2 studies of Busulfex, the autologous and the allogeneic study, demonstrate: (a) adequate evidence of myeloablation and engraftment?

DR. PAPADOPOULOS: Yes.

DR. DUTCHER: All those who would vote yes?

[Show of hands.]

DR. DUTCHER: Fifteen yes, zero no.

(b) Do they demonstrate adequate evidence of safety?

Comments, answers?

DR. MILLER: I think their data on VOD and their data on toxicity with the definitions set out and looking at in the Phase 2 setting appear adequate.

DR. DUTCHER: So, we are basing safety data on 100 patients in these studies.

DR. SANTANA: I would comment that it is still unknown in children. I don't know if that is a global statement or a unique statement, but we need to be careful.

I don't think there is enough data in children that we can make that comment as a generalized comment for all patients.

DR. MILLER: I agree.

DR. DUTCHER: All those who would vote yes for adequate evidence of safety, raise your hand.

[Show of hands.]

DR. DUTCHER: Fourteen yes.

No?

[One hand raised.]

DR. SANTANA: No, because I think there is no data on children that has been reported.

DR. DUTCHER: One no.

DR. PAPADOPOULOS: Will there be an age limit, though? I mean in the labeling, there will be some recommendation as to use in --

DR. J. JOHNSON: The company is asking for approval in adults, limiting it to adults.

DR. DUTCHER: So, until there are data, then, it will be limited to adults.

2. Pharmacokinetics. Is the pharmacokinetic profile of Busulfex Injection: (a) Similar to oral busulfan and (b) is superior to oral busulfan?

Does anybody want to discuss this or do you want to just vote? Vote. Okay.

Is it similar to oral busulfan? Any comments?

[No response.]

DR. DUTCHER: All those who would vote yes?

[Show of hands.]

DR. DUTCHER: 15 yes, zero no.

Superior to oral busulfan? I guess we answered that, didn't we. Okay. So, I can assume that it's the reverse? Okay. Zero yes, 15 no.

3. Does the literature review demonstrate substantial evidence of the safety and efficacy of oral busulfan-containing chemotherapy regimens in stem cell transplantation for the following:

(a) chronic myeloid leukemia?

Dr. Sledge.

DR. SLEDGE: I would like to kind of know what we are being asked to discuss here, because I heard two different things in the FDA presentation.

One was a comparison of two different transplant regimens, and the other was the question of whether or not, for specific diseases, transplant was beneficial at all, and there were times in the presentation where I wondered whether or not Don Thomas was going to have to give back his Nobel prize.

I guess my general question is which of those two questions are we being asked to address here.

DR. J. JOHNSON: We are not being asked to address

whether bone marrow transplantation is safe and effective for these conditions. We are being specifically asked whether bone marrow transplantation with busulfan-containing regimens is safe and effective for each of these conditions.

DR. DUTCHER: I think the other comment to be made is that the data for AML that was presented was in first CR primarily, so that I think there should probably be some stipulation for things like this.

DR. J. JOHNSON: You know, if you want to have a separate vote, break that down into subgroups, fine.

DR. PAPADOPOULOS: I think that the point needs to be made that AML is a very, as we know now, heterogeneous disease. It is no longer considered just AML. There are clearly subgroups that at least potentially would benefit from bone marrow transplantation and are known to have inferior survival with chemotherapy, and on the other end there are clearly groups that appeared to do better with dose-intensive chemotherapy.

Are we going to begin to break the indications down in labeling or leave it up to the investigator?

DR. DUTCHER: Dr. Temple.

DR. TEMPLE: Drugs are generally approved for specific uses. Cancer chemotherapeutic agents are approved for specific diseases, specific stages, et cetera. The quirk here is the real claim is that it is a substitute for

the other stuff you are using, but that would amount, if you didn't pay attention to the specific diseases, to approving busulfan for a variety of things without clear evidence that it is effective and that drugs are approved for specific things in general.

So, it is relevant, and you will notice that we are in no sense asking a standard that would ordinarily be the basis for approval. I mean we haven't probed all those studies and looked at them, and done the usual things.

The question is whether there is reasonable evidence for usefulness in a particular setting.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: Just to make it even more complicated, before we start voting disease by disease, I would ask the FDA that if you come up with an indication for one or two rather than all five of these, whether there would also be some flexibility about an indication for patients with other diseases who are felt to benefit from transplants, but who are not candidates for some of the standard -- even though we recognize that the standard conditioning regimens have never been FDA approved as such.

DR. TEMPLE: The standard regimens now in use have never been approved by the FDA as such. Obviously, physicians know that they can use the drugs that way, and the reality is if it is available for any one of those uses,

people will figure out that they have decided busulfan is appropriate in this setting or that setting, and do it.

Nonetheless, we worry about -- I mean, for example, you could imagine something that says use in transplant settings. Well, that would be a sort of -- that would be like labeling any standard cancer drug "use in cancer." Would that be silly or would we feel comfortable with that? We have historically, probably for good reason, gone case by case, and it is hard to see why one would not bring the same kind of thinking here.

I emphasize again we haven't asked people to bring forth data, show us all the trials and stuff, except as we can determine it from the literature. So, it is a somewhat lesser standard than usual we have to acknowledge.

Do you guys want to add anything?

DR. MILLER: When you initially met with the sponsor, I mean how did you define what they were expected to get out of literature search before they undertook -- because I mean you have had meetings with them -- did you say you were going to require a randomized trial or other information, because I think you build on something in your initial pre-NDA meeting.

I guess the other statement is that a goal of a preparative regimen is threefold - immunosuppression, myeloablation, and thirdly, antitumor effect. It is part of

a regimen that includes other modalities, as well, so I think there are reasons why it is being asked to do, sort of like to do two things, to myeloablate and to immunosuppress to allow engraftment. So, it is different.

DR. TEMPLE: Isn't it supposed to have some effect on the tumor cells?

DR. DUTCHER: No.

DR. PAPADOPOULOS: No, not necessarily. I mean that is the point. This is a treatment modality, it's a package. Although there have been isolated transplant settings where busulfan has been used as a single agent, a high dose busulfan for autologous transplants in CML or in syngeneic transplants for CML, the rest of the transplant experience in literature is all based on a package, busulfan in combination with something, and it is a treatment modality.

I don't think you can compare it to the evaluation and approval process for a chemotherapeutic agent which has specific indications and specific diseases based on efficacy trials. At least in the allogeneic setting, you also have to take into account the different effects of graft versus leukemia on the different malignancies.

DR. TEMPLE: Let's say you are taking it as a package. We understand that in a lot of cancer chemotherapy, you don't always get to tease out the

contribution of each component very well, but you do ask that the combination have a beneficial effect, don't you? Doesn't that matter?

DR. DUTCHER: It does, but I think you can argue in this setting that alkylating agents are not particularly a good anti-leukemic drug. They may be good for lymphoma or some of the B cell disorders. Historically, when we have alkylating agents at non-transplant doses, it didn't do anything to the disease except make the bone marrow go away and come back with leukemia.

So, in this setting, you really are doing something else. You are giving a drug -- they are the safest drugs to escalate to very advanced doses, so you are giving high doses of something to myeloablate, to immunosuppress, to allow either the person's own marrow to grow back or transplanted marrow.

So, it is a little bit different. I mean I think even people who are not as I guess comfortable with all of these indications for transplant would say that it is a different role than simply a drug that is good for diseases, it's for the process.

Dr. Schilsky.

DR. SCHILSKY: Just to follow up on that, would you suggest then that as we consider these various indications, we consider whether the source of the stem

cells is autologous or allogeneic? The argument that you just made is that busulfan-containing regimens is part of a program of allogeneic transplantation that may be effective.

In the autologous setting, though, one might have to consider the strict antitumor effect because there is no other effect with respect to treatment of the underlying malignancy that one could invoke.

DR. DUTCHER: I think that is the argument that the randomized studies have made between HDAC and autologous transplant, you know, versus autologous.

DR. SCHILSKY: I am just trying to clarify what the various positions are because I don't think that, on the one hand, we can say yes, this is a component of a total treatment program and may be only a minor component with respect to antitumor effect, and then, on the other hand, say, oh, and by the way, if you give autologous stem cells where it is the major component of antitumor effect, that is okay, too.

DR. DUTCHER: Dr. Simon.

DR. SIMON: My position would be it is a component of a package, but I don't see how you could approve it unless you have adequate evidence that the package is effective for the patient.

I think, as I understand it, that is all that is being asked, and whether the package is effective for the

patient depends upon the disease. In other words, if transplants are being given in AML, in a situation where chemotherapy is better, standard maintenance chemotherapy, then, the package is no good and it shouldn't be approved for that indication.

DR. MILLER: But it gets more difficult. There are subgroups of patients with AML without --

DR. SIMON: Then, they need to demonstrate the case for what subgroups is it effective, and they haven't done that.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I think along the same lines, that it may be the modality of transplant is more important for this indication than the disease. I mean AML may be where we get broken down in our vote, but certainly we know that for CML, we need the drug, we need the immunosuppression, and we need the GB malignancy for really optimal control.

In AML, we don't know exactly what we need, but I think we would agree that autologous busulfan-based transplants for AML are not going to be the answer, and I still think we need to focus on allo and URD versus auto at maybe the break point, and not ignore it.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: Would you feel comfortable adding a category of patients who require transplant who can't have

TBI, and would that make people feel better, or is there just not enough evidence even in that subcategory?

DR. MARGOLIN: I think Dr. Temple has told us that that would be the exception rather than an indication, and that that doesn't fulfill the regulatory requirement.

DR. TEMPLE: Well, I don't want to be absolute about that. I am just saying what has been usual. For example, we have contemplated drugs to protect against toxic effects of other drugs, and initially, with the help of the committee, we have taken the position that you need to look in each setting because you are worried about protecting the tumor, but at some point -- and we have put this in a document -- if you got the idea that it didn't protect the tumor from several settings, we would then write it as decreases cisplatin toxicity.

I guess I am personally sympathetic to what Rich said. You sort of need to know whether the whole package is good, and then this has its role in it, but I wouldn't say that is the only conceivable position. So, we need your input on this.

DR. MARGOLIN: Then, maybe what we should do actually would be vote disease by disease and type of transplant for that disease by type of transplant, unless it gets too cumbersome.

DR. TEMPLE: That is sort of what we were inviting

you to do, but other people have put forth a different concept, and certainly at some point there should be discussion of that, too.

DR. DUTCHER: I also think that there are certain requirements for additional studies that need to go into this in terms of trying to understand both the modality and the effectiveness in subsets, but, you know, subsets get to be tiny numbers. That is part of the problem.

Do you want to vote disease by disease, try it out and see how we go? Okay.

It is based on the literature reviews that we have seen in both packages.

Does the literature review demonstrate substantial evidence of the safety and efficacy of oral busulfan-containing chemotherapy regimens in stem cell transplantation for chronic myelogenous leukemia?

All those who would vote yes?

[Show of hands.]

DR. DUTCHER: 15 yes. Zero no.

For acute myelogenous leukemia in the allogeneic setting, all those who would vote yes?

[Show of hands.]

DR. DUTCHER: 5 yes.

All those who would vote no?

[Show of hands.]

DR. DUTCHER: 6.

All those who would vote abstain?

[Show of hands.]

DR. DUTCHER: 3.

Does the literature review demonstrate substantial evidence of the safety and efficacy of oral busulfan-containing chemotherapy regimens in stem cell transplantation for autologous transplant in AML?

All those who would vote yes?

[One hand raised.]

DR. DUTCHER: 1 yes.

All those who would vote no?

[Show of hands.]

DR. DUTCHER: 12 no.

All those who would abstain?

[Show of hands.]

DR. DUTCHER: 2.

Allogeneic AML, we have to go back.

All those who voted yes for allogeneic AML?

[Show of hands.]

DR. DUTCHER: 5.

All those who voted no?

[Show of hands.]

DR. DUTCHER: 7 no. Okay. And 3 abstentions.

For acute lymphocytic leukemia, all those who

would vote yes?

[No response.]

DR. DUTCHER: Zero.

Vote no?

[Show of hands.]

DR. DUTCHER: 15 no.

Myelodysplastic syndrome?

All those who would vote yes?

[Show of hands.]

DR. DUTCHER: 4 yes.

All those who would vote no?

[Show of hands.]

DR. DUTCHER: 7.

All those abstaining?

[Show of hands.]

DR. DUTCHER: 4.

Malignant lymphomas? Are we talking allo or auto? Both. Allo transplant malignant lymphoma.

All those who would vote yes?

[Show of hands.]

DR. DUTCHER: 3.

All those who would vote no?

[Show of hands.]

DR. DUTCHER: 12.

Auto malignant lymphoma.

All those who would vote yes?

[Show of hands.]

DR. DUTCHER: 3 yes.

All those who would vote no?

[Show of hands.]

DR. DUTCHER: 12 no.

Is the NDA for Busulfex Injection approvable?

All those who would vote yes?

[Show of hands.]

DR. DUTCHER: 15 yes.

So, after all that torture, we have come up with it appears approvable for CML based on the evidence in the literature that was presented and which seems to be a level that people are comfortable with, mixed votes in acute myeloid leukemia and in myelodysplasia, and less mixed in lymphoma and no data in ALL.

We will now take our luncheon break. Let's try to start promptly at 12:30.

[Whereupon, at 11:15 a.m., the proceedings were recessed, to be resumed at 12:30 p.m.]

AFTERNOON SESSION

[12:30 p.m.]

DR. DUTCHER: I appreciate the sponsor's willingness to move up their timetable and get people here. What we will probably end up doing is splitting the open public hearing around the sponsor's presentation, taking the people that are here first, and then if we need to, we will go back and get the rest of them after you have finished. It just depends on how many people are here.

Before we start, I want to just introduce the members of the committee once again, because there are some new people at the table.

Could we start with Dr. Simon.

DR. SIMON: Richard Simon, National Cancer Institute.

DR. ALBAIN: Kathy Albain, Medical Oncology, Loyola University, Chicago.

MS. BEAMAN: Carolyn Beaman, Sisters Breast Cancer Network, and Consumer Rep to the committee.

DR. SCHILSKY: Rich Schilsky, Medical Oncologist, University of Chicago.

DR. SLEDGE: George Sledge, Medical Oncologist, Indiana University.

DR. RAGHAVAN: Derek Raghavan, Medical Oncologist, University of Southern California.

DR. FORESTIERE: Arlene Forestiere, Medical Oncologist, Johns Hopkins.

DR. KROOK: Jim Krook, Medical Oncologist, Duluth CCOP.

DR. DUTCHER: Janice Dutcher, Medical Oncologist, New York Medical College.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the committee, FDA.

DR. D. JOHNSON: David Johnson, Medical Oncologist, Vanderbilt University.

MR. GRUETT: Glenn Gruett, a cancer survivor from Appleton, Wisconsin.

DR. NERENSTONE: Stacy Nerenstone, Medical Oncologist, Hartford, Connecticut.

DR. SANTANA: Victor Santana, the only Pediatric Oncologist, St. Jude's Children's Research Hospital.

DR. KOBAYASHI: Ken Kobayashi, Medical Oncologist, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology Drug Products, FDA.

DR. DUTCHER: Thank you.

Open Public Hearing

DR. DUTCHER: We will now proceed with the open public hearing. We do have some written material from a number of people that is available at the desk also for

those of you that want to look at them.

The first speaker will be Allen Robinson.

[No response.]

DR. DUTCHER: Ted Kanakis.

[No response.]

DR. DUTCHER: Pier Cipriani. We will start with you, sir. Thank you. Please use the microphone, identify yourself, and any support from the sponsor.

DR. CIPRIANI: I am Pier Cipriani. I am a dentist. I have no connection to Zila, the sponsor, other than the fact that I do own stock in the company.

My father died from a primary oral cancer. Over a five-month period, neither his dentist nor his physician had noticed a lesion growing on the floor of his mouth. In the 11 months that followed, two major surgeries and radiation treatments left him severely debilitated, disfigured, and in excruciating pain. That final period of my dad's life, following late stage detection of oral cancer, was certainly a living hell for him and for those of us who loved him. I wanted to spare others this type of agony.

I learned that Dr. Arthur Mashberg had demonstrated superior oral cancer detection results using toluidine blue as an oral rinse in a two-stage application procedure. The NIH has been issued a patent for what is known as the Mashberg protocol.

My colleagues and I obtained an exclusive license for the patent and began working to create a test kit based upon it. We subsequently transferred our rights and interests to Zila, Inc., which perfected the OraTest product.

U.S. dental schools have for decades taught that toluidine blue can be used to detect and define the margins of squamous cell carcinoma in the oral cavity. Why aren't dentists using this technique? Because when toluidine blue is ordered from a chemical supply house, it arrives as a reagent grade powder in a jar labeled "Not for Human Use."

When the powder is put into an alcohol solution, the liquid is a potent dye, capable of even staining ceramic. Preparing the solution stains fingers, clothing, and countertops. The resulting liquid has a shelf life of only one to two days.

Worse still, impurities and inconsistencies in concentration of toluidine blue abound in the various reagent grade products labeled "toluidine blue," so staining results may vary from batch to batch.

To overcome these barriers to use, OraTest has pure, pharmaceutical-grade ingredients, ready to use, pre-mixed and flavored solutions, and a multi-year shelf life. Instructions for use incorporate the NIH/Mashberg protocol, reducing false positive results to fewer than 10 percent.

The staining material in OraTest, Zila's tolonium chloride, is the only toluidine blue manufactured under GMP conditions.

Zila has produced a wealth of documentation demonstrating that OraTest is effectively 100 percent sensitive to squamous cell carcinoma. This, as you know, is the critical issue. Some would argue that toluidine blue has a history of high false positive rates. I want to underscore, first, that OraTest directions for use are based on the NIH patent, which reduces false positives to under 10 percent, and second, as all of us in the healing sciences know, no one ever died from a false positive.

My profession has not done its part to screen adequately for oral cancer. The Journal of the American Dental Association noted in August 1997 that in one study, only 42 percent of dentists reported performing a standard head and neck exam.

A CDC survey reported that only 15 percent of people over 40 who visited a dentist ever recalled having had an oral cancer exam. Is it any wonder that for 40 years, U.S. oral cancer survival rates have been stagnant at close to 50 percent? Or that today, more than one American dies every hour of this disease?

The ADA Journal's editor in chief wrote, "For a disease that is dentistry's to prevent and to treat, we have

demonstrated a singular lack of progress in controlling the occurrence of oral and pharyngeal cancer.

Think of the impact the Pap test has had on cervical cancer detection. The PSA test has accomplished the same for early prostate cancer detection. The pending FDA application to use toluidine blue O as an adjunct in detecting oral malignancy may provide an early step in this direction.

The key then to reducing oral cancer morbidity and mortality is early detection. Survival rates for early stage lesions exceed 80 percent, while those with advanced disease have only an 18 percent survival rate. Once a lesion is clinically apparent to a visual and digital exam, it has become relatively large and probably has metastasized, which is the case with over 50 percent of oral cancer when first diagnosed.

Small, innocuous lesions are easy to overlook, and those that are noted may often be dismissed as something that should be "watched," which too often means ignored and forgotten.

Recent studies have shown that even highly experienced oral cancer experts missed large percentages of cancerous lesions that were subsequently detected with OraTest. Some will say that dentists don't have access to high-risk patients.

The ADA Journal reports that 25 million adult smokers see a dentist at least once a year, and many more of the nation's 10 million spit tobacco users, and additional millions of heavy drinkers do the same. The issue for many is not access to health care, but accuracy in detection and diagnosis.

When Babe Ruth complained of gross symptoms stemming from nasopharyngeal cancer, he was first misdiagnosed with sinusitis, then had three teeth extracted and was subjected to repeated rounds of oral tissue biopsies, all of which yielded false negative reports.

Brett Butler, the Baseball Hall of Famer, had his oral cancer treatment delayed due to a misdiagnosis of tonsillitis. Singer Burl Ives didn't know he had oral cancer until it was discovered by physicians prepping him for back surgery.

Presidents Ulysses S. Grant and Grover Cleveland, Beatle George Harrison and even the Dapper Don John Gotti have experienced oral cancer, and could have benefitted from this remarkably simple, accurate, and inexpensive diagnostic adjunct.

In other countries, OraTest use reportedly is changing tobacco and alcohol habits. OraTest may help the U.S. reach the Federal Government's Healthy People 2000 objective to "increase to at least 75 percent the proportion

of primary and oral care providers who routinely advise tobacco cessation."

With OraTest and appropriate professional support and education, dentists will be more likely to perform thorough oral cancer exams on appropriate at-risk patients. The OraTest exam technique has already been endorsed by the 600,000 member FDI World Dental Federation and the British Dental Association, and surely more endorsements will come in this country once approval is granted.

OraTest will increase the rate of early detection of oral cancer, save lives, improve the quality of life of oral cancer survivors, and significantly reduce the estimated $3.7 billion financial burden that oral cancer imposes on our entire society today. For that I will be proud to have played a small part, and I ask that you allow this to happen. It is long overdue.

Thank you.

DR. DUTCHER: Thank you very much.

The next speaker is Stephen Corbin.

[No response.]

DR. DUTCHER: Phillip Bonner. Thank you.

DR. BONNER: I am Phillip Bonner, President of the Oral Health Education Foundation. I am a dentist. I would like to state that we receive funding from many organizations, and have received educational grant

unrestricted funding from Zila in the past. All of the expenses for me to come here were paid by the Foundation and no outside organizations.

The Oral Health Education Foundation is a 501(c)(3) public nonprofit foundation. We are based in Atlanta with staff in New York City. Our goal and our mission is to improve the oral and related systemic health of the public through educationally based programs, both to a public and a multidisciplinary professional audience.

Our most aggressive program to date is the National Oral Cancer Awareness Program, or NOCAP, which was launched in 1994 with the production of a video entitled, "What You Should Know About Oral Cancer," which featured a very poignant segment by Cal Ripken, Jr. of the Baltimore Orioles.

Since that time, we have produced additional videos on oral cancer and related topics. We have published a written Course Guide that is used by the National Federation of State High School Associations to teach a class on oral cancer.

We have launched and maintained a very extensive web site on the internet, at www.oralcancer.org. We are working with numerous groups, such as the Oral Cancer Roundtable, to deal particularly in the areas that we feel are important in prevention and early detection. These are

the two areas we feel will have the most impact on reducing the mortality and incidence and morbidity associated with oral cancer.

When we look at facts and statistics related to oral cancer, there are several that I think are very pertinent to this committee's deliberations. I know some have been mentioned already today, but only 53 percent of patients survive more than five years with oral cancer. The vast majority of oral cancer cases in the U.S. are associated with tobacco use or heavy alcohol use, or particularly the combination of the two, but it is important to note that there is still a significant number of cases that are not associated with these causative factors and more research is needed to determine other causative factors for oral cancer.

If oral cancer is detected early, as we know, before it spreads, survival rates increase dramatically, but as Dr. Cipriani noted, if the disease is detected at later stages when it has metastasized, survival rates drop to as low as 18 percent.

At present, the detection of oral cancer relies mainly on clinical observation and palpation. Certain definable populations in the United States have a significantly higher incidence of, and mortality from, oral cancer. For example, black males have twice the incidence

and mortality than white males. Patients who have been treated for oral cancer has a significant risk for the development of secondary lesions.

These facts lead us to identify certain major needs that we have in terms of dealing with oral cancer as a significant public health risk. These include the need for a more objective, standardized method for detecting oral cancer at the earliest possible stage of the disease, so that different examiners in varying locations, including globally, can achieve standardized results.

We need aggressive prevention programs aimed at at-risk populations. We need an oral cancer detection system that is easy to use and will act as an incentive to health care professionals to conduct oral cancer examinations of at-risk populations.

We need a detection system that produces fast, accurate results and is comfortable for patient use, so that at-risk individuals, including current oral cancer patients at risk for secondary lesions, will be encouraged to seek examination.

We firmly believe that OraTest offers a much needed method for increasing the objectivity and standardization of the oral cancer examination process. The sensitivity of the system its easy of use, its rapid results produce a user-friendly, accurate test that will act as an

incentive to both professionals and patients to examine for the disease.

OraTest will provide a system for examining at-risk populations and detecting oral cancer at earlier stages than is often possible using our current methodologies. OraTest also increases the accuracy of the biopsy process by more clearly delineating lesions.

The existence of a quantifiable test that yields visual results in a short period of time, while the patient is still present, should serve as not only an incentive for examination, but also as a powerful preventive tool, particularly in terms of tobacco and/or heavy alcohol use.

In addition, OraTest should serve as a valuable tool in conducting clear outcome studies for validation of various oral cancer treatment modalities.

As Dr. Cipriani mentioned, the Pap smear represented a major advance in the detection of cervical cancer when it was introduced and still remains a standard of care today. Today, oral cancer kills twice as many Americans each year as cervical cancer.

OraTest is significantly more sensitive than Pap smear, and our serious need for an accurate, standardized method for detecting the disease at its earliest possible stage can be met if OraTest is approved for use in this country.

The benefits will hopefully be a reduction in the devastating mortality and morbidity associated with this disease.

I appreciate the opportunity to present.

DR. DUTCHER: Thank you very much. We appreciate it.

Thank you both very much for your comments. Have any of the other public speakers arrived? Mr. Robinson, Mr. Corbin, Mr. Kanakis.

[No response.]

DR. DUTCHER: I think what we should do is proceed with the sponsor's presentation and then we can ask them to speak when you have finished. Thank you.

NDA 20-765 OraTest (tolonium chloride)

Zila, Inc.

Sponsor Presentation

Introduction

Ralph Green, D.D.S.

DR. GREEN: Thank you, Dr. Dutcher. My name is Dr. Ralph Green. I am President of Zila Biomedical. I want to thank the Division of Oncology Drugs and the members of the panel for being here today and allowing us to present an overview of our NDA of the OraTest product.

OraTest is toluidine blue, a chemical that has been used in various medical applications, first reported in

the early 1960s. The product we are using today is variously named OraTest, OraScan, OraScreen in its marketing around the globe. It is a 20-second mouth rinse which contains three, 20-second gargles with the solution.

Solution 1 and Solution 3 are acetic acid with a raspberry flavoring, which patients liken to raspberry vinaigrette. The 20-second mouth rinse, which has the active ingredient, contains our 1 percent toluidine blue.

The active ingredient, our proprietary form of toluidine blue is known as Zila's tolonium chloride. It stains abnormal cells a royal blue to promote the early detection of squamous cell carcinoma, an adjunct to head and neck examination.

The regulatory history for Zila started with a 510(k) submission for medical devices in 1991. After meeting with the FDA ombudsman, the company was informed that the product would be regulated, not as a device, but as a drug, and that Zila should submit its data to the Division of Medical Imaging, Surgical, and Dental Drug Products.

Two different acting directors of that division advised Zila in writing that the published literature appeared to support the filing of a paper NDA. One week prior to this presubmission conference, the meeting was canceled and Zila was directed to reschedule the meeting with the Oncology Division.

When we met with the Oncology Division, there was a sudden departure from the prior assurance that the literature was acceptable. Our aim today is to clarify what we believe are the FDA misconceptions about our product and about our data, which we have shown in our clinical study to be 100 percent sensitive.

We also have a p value of 0.004. Indeed, even considering the worst case interpretation of the data that was presented by the FDA medical officer, the sensitivity for OraTest has been described by that medical officer as 0.89.

We also believe that this data supports the proposed indication for use. The objective that we have established will be presented to you, and has been presented to you in two pivotal studies.

The first pivotal study was done by Dr. Joel Epstein at the Vancouver Cancer Center, and was published in the Journal of Oral Surgery, Oral Medicine, and Oral Pathology.

The second pivotal study is Zila's multicenter study, which came out of the meeting with the Oncology group. It is an IND Study 44-389. It involves 12 centers around the world, 10 in the United States, 1 in Canada, and 1 in the U.K.

The Zila clinical protocol calls for two

independent examiners who look at the patient on visit one. The first examiner does a visual examination, and is abundantly aware that there will be a second examiner who will also examine this patient.

The second examiner then uses the tool OraTest to examine the patient, and vice versa. If anything, high risk status of patients that are in the ongoing followup, the first examiner is not biased to miss any visual lesions, and that is critical.

Also, in this particular study, the central lab that evaluates the pathology is also blinded from the local lab. We believe our clinicians will demonstrate the need for this diagnostic adjunct and how this interim data that we have been gathering in IND 44-329 has come to be used as support for future screening claim, that we can properly use this data to support the diagnostic adjunct for site selection.

It is our respected belief that the FDA's review of the NDA fails to appreciate the proper context and content of our data. In the course of our presentation today, we look forward to assisting you in answering the questions that have been placed before you.

Our presenters today are Dr. Rowena Dolor, Dr. Sam Bernal, Dr. Stephen Porter, Dr. Roy Feldman, Dr. Joel Epstein.

As you listen today, I want you to remember that there has not been an issue of safety in this product from the beginning.

Dr. Dolor.

Background and Incidence of the Disease

Rowena J. Dolor, M.D.

DR. DOLOR: I am Dr. Rowena Dolor. I am a general internist at the Durham Veterans Affairs Hospital, as well as Duke University Medical Center.

[Slide.]

Today, I am going to talk about the role of OraTest in aiding the physicians in their head and neck examination. I just want to thank the two public speakers that have sort of made my job easier in presenting some of my introductory data that I am going to present.

[Slide.]

I want to start by mentioning the incidence of oropharyngeal cancer in comparison to some of the other major carcinomas. As the speaker has mentioned, there are over 30,000 new cases or 8,000 deaths due to oropharyngeal cancer annually, many of these cancers for which we clinicians screen, have an adjunctive diagnostic test.

For example, in breast cancer, we use the self-breast exam, the clinical examination, as well as the mammogram to help detect carcinomas.

The incidence of oropharyngeal cancer, as the public speaker has mentioned, is higher than that of cervical cancer, because now we have the Pap smear as a diagnostic test to help identify lesions. The incidence of cervical cancer was similar to that of oropharyngeal cancer before the diagnostic use of the Pap smear.

[Slide.]

Just as a review, and I will go over this quickly because I know you know these statistics, the median age of patients who present with oropharyngeal cancer is 64 with 95 percent of patients presenting over the age of 40.

These rates of oropharyngeal cancer are rising in females, as well as in minorities, as they begin to smoke tobacco. The rates used to be more like 6 to 1 in the 1950s, and now the male to female ratio is now 2 to 1.

The five-year survival has been mentioned. It is 55 percent overall with better survival for localized disease, and worsening survival, as well, for metastatic disease.

[Slide.]

In summary, the incidence of oropharyngeal cancer can be put down in this fashion. In the general U.S. population, there are 11 to 17 cases per 100,000 patients. In high-risk, asymptomatic patients, the incidence is higher more like 1 out of every 200 to 250, and in those with a

history of an upper aerodigestive tract tumor, the incidence of recurrent oropharyngeal cancer or a secondary primary cancer in the oropharynx is more of 1 out of 7.

[Slide.]

Right now what we have for screening is careful visualization and palpation, but we know that from the dental literature, that the sensitivity and specificity of visualization and palpation alone is poor.

In the medical arena, we know that there are physicians, front-line physicians like myself in primary care, who do an abbreviated examination within a room with inadequate lighting to look at the subtle changes of the oral mucosa, which are the early signs of oropharyngeal cancer. The accuracy of our abbreviated examination is relatively unknown.

Erythroplakia is the more common precursor for oropharyngeal than leukoplakia. Ninety percent of biopsies of leukoplakia are benign, whereas, 90 percent of biopsies of erythroplakia are either dysplastic lesions or carcinoma.

Dentists may be more effective than physicians in identifying lesions, early oropharyngeal carcinoma lesions, however, physicians are still important in the screening of oropharyngeal cancer because we gain access to the high-risk populations.

Dr. Cipriani mentioned that 25 million Americans

are smokers reported having seen a dentist in the past year as part of the cancer control supplement to the 1992 National Health Interview Survey, but 70 percent, or 34 million, of those smokers reported seeing a physician in the past year.

[Slide.]

The screening recommendations are mixed by the different societies. The American Cancer Society recommends screening every three years for those over the age of 18, but yearly for those over the age of 40.

The Canadian Task Force, in looking at the evidence, says there is insufficient evidence to include it or exclude it as part of the annual exam, however, they do recommend an examination for those at risk.

The National Institutes of Health previously recommended screening for oropharyngeal cancer, but then switched it a couple years ago to just screening during a routine dental examination.

[Slide.]

The U.S. Preventative Task Force, in their 1996 guideline, have said that it is a Level C recommendation where there is insufficient evidence to include it in routine screening of asymptomatic patients.

They do recommend secondary prevention by screening patients that are at risk, encouraging patients to

receive regular dental examinations, offering counseling for tobacco and alcohol cessation as primary prevention, as well as protecting skin and lips from sun exposure.

[Slide.]

The role of OraTest in the head and neck examination is as an adjunct to the visual examination of the oropharynx. The incidence of oral cancer is such that it is not practical to design a clinical study involving a broader population with oral lesions suspected or known to be malignant.

As I have shown in previous slides, the incidence of oropharyngeal cancer in such individuals in too to make a clinical study affordable.

The population of the Zila study was selected for the high incidence of oral cancer in a population that has already been treated for upper aerodigestive tract tumors. The objective of that study is to establish a basis for a screening claim in that population.

The proposed claim for this NDA to a population of patients that have oral lesions suspected or known to be malignant is for the sole purpose of limiting the use of the product to those patients that are already candidates for a biopsy, and therefore, the benefit of a biopsy site selection aid poses no additional risk.

Alternatively, if an additional biopsy site is

indicated by a positive stain at a satellite lesion, the additional risk would be minimal. Limiting the use of OraTest on the indicated population to improve site selection is a pure benefit to both the patient and the clinician.

As subsequent presenters will make clear, proper biopsy selection within an area of diseased tissue that is both observable and suspicious is not trivial. The discovery of any additional carcinoma or carcinoma in situ that is not apparent by visual observation is a clear benefit.

The clinical literature regarding toluidine blue has contained occasional references over the past 30 years of lesions being detected by toluidine blue that were not visually observed. The interim analysis of the Zila multicenter clinical study documents thoroughly and convincingly show that invasive carcinoma and carcinoma in situ exists at significant levels which cannot be discerned by visual observation.

We think that the absence of an early detection mechanism is largely responsible for the poor five-year survival rate for oral cancer victims. The lack of an early detection is not due to clinician incompetence or indifference.

In the absence of a diagnostic tool like OraTest,

confirmable cancers are able to progress undetected because there is no apparent lesion or other symptoms capable of being detected.

With availability of a diagnostic tool like OraTest, we anticipate that OraTest will increase the number of appropriate and early referrals to dental and otolaryngology clinics.

With early detection, we can improve survival and reduce morbidity from the current modalities that we have available for treatment, morbidity from disfigurement, dysphasia, dysarthria, and xerostomia.

Reducing morbidity will improve the quality of life in patients who are living with oropharyngeal cancer.

Thank you.

Chemistry and Mechanism of Action of Toluidine Blue

Samuel D. Bernal, M.D., Ph.D.

DR. BERNAL: Good afternoon. My name is Sam Bernal. I am a medical oncologist and a professor at UCLA.

[Slide.]

I have been doing studies in the laboratory on cationic dye uptake since 1982. This was in collaboration with Dr. Lam Bo Chen at the Dana Farber Cancer Institute at Harvard. More recently, Zila approached me to extend their clinical studies on the early detection of oral cancer which

you have instituted starting in November of 1998 in several UCLA-affiliated hospitals.

My task today is to review the basis for the selectivity of staining of carcinoma cells in general and oral carcinoma in particular.

[Slide.]

In my laboratory, there are three systems that we study, all of these three systems relevant to this presentation are vital stains, that is, on living cells. One, we examine the staining characteristics of oral carcinoma cell lines along with other carcinomas.

We also look at fresh isolates of different carcinomas including oral cancer. We also do thin sections of oral lesions that then are initially stained by a cationic dye, but emphasizing that this same section is later on stained by standard histopathologic stains.

What we have found is that toluidine blue selectively stains living carcinoma cells. The basis of selectivity is retention by carcinoma cells, and this we find by the following procedure, which is analogous to the clinical procedure of OraTest.

Basically, either the cell lines, the fresh isolates, or the tissue sections are maintained in culture medium. This is RPMI with 15 percent fetal calf serum, 1 millimolar of glutamine kept at 37 degrees. They are then

exposed to stain for 20 seconds followed by dye-free medium rinses for 20 seconds, and then examined either by light microscopy or by fluorescence microscopy in the case of other cationic dyes.

The carcinoma cells do have some advantage in terms of uptake of the dye initially, but the major difference between carcinoma cells and normal epithelial cells is the amount of dye that is retained after the rinse.

[Slide.]

The major distinguishing factor that I would like to make is between live cell and fixed cell staining. In live cells, toluidine blue, along with other cationic dyes, are concentrated in mitochondria.

In living cells, the mitochondria appear as long and filamentous, branching structures, whereas, in fixed, permeabilized cells, the dye does not stain mitochondria. Instead, it is concentrated in nuclei and nucleoli consistent with previous publications that the dye binds to RNA and DNA.

[Slide.]

In contrast to the vital stain that has specificity for carcinoma cells, fixed cell staining is nonselective because normal epithelial cells, fibroblasts are stained as well as carcinoma, and again, nuclei and nucleoli are stained.

The mitochondria are visible, but not stained. They appear short and oval, which is purely an artifact of fixation, and not relevant to the OraTest.

[Slide.]

The issues then that we had to address again with toluidine blue, but also with other cationic dyes, is why does it stain living cells, why carcinoma cells, and why specifically mitochondria, and why is the dye selectively retained.

[Slide.]

Toluidine blue species are part of a group of compounds. They are really tricyclic heteroaromatic dyes. They are composed of three rings, in other words, with delocalized positive charges. They are water soluble, but they are also lipophilic, which means that they penetrate membranes well.

[Slide.]

Toluidine blue is part of this class as being a representative of the thiozine group. Included with this group is pyronin Y of the xanthene class, and rhodamine 123 of the rhodamine class. These latter two compounds I mention because some of the members of the panel may be more familiar with their use.

Rhodamine 123 is a particular stain that we have used many years ago and up to now to stain carcinoma cells

specifically.

[Slide.]

The retention in mitochondria is only with positively charged compounds, analogs with negative or neutral charges are not concentrated in mitochondria and will not stain carcinoma cells specifically.

The retention of the dye is dependent upon the electronegative charge of mitochondria, and we have found by independent studies that the mitochondria of carcinoma cells and oral cancer in particular is much more negative on the inside compared to normal oral epithelial cells or fibroblasts.

Of the oral carcinoma cells that we have isolated as fresh isolates or of the cell lines of oral cancer that we have looked at for mitochondria charge and selective retention of cationic dyes, 100 percent of them are strongly electronegative and selectively retain the dye.

Mitochondrial poisons and any other damage to the cell that eliminates the electrical charge of mitochondria will cause release of the dye.

[Slide.]

The mitochondria of carcinomas, of oral cancer, is not unique because other carcinomas of the head and neck are also selectively retained of this dye. Lung carcinomas also have the same characteristic, squamous, adeno, and large

cell. An exception is small cell carcinoma of the lung. That does not retain the dye.

Breast cancer, bladder cancer, colon cancer, and cervical cancer, for that matter, also retain the dye.

Those cells that do not retain the dye are normal epithelial cells, fibroblasts, lymphocytes, and macrophages, and it is also not retained well in cancers of connective tissue origins, such as sarcomas, those of lymphatic origin, lymphomas, and those with neural characteristics, the neuroblastomas.

In conclusion, there is a strong scientific basis for the staining of carcinoma cells selectively compared to normal epithelial cells, and in our clinical study that has been extended now to Southern California, we are continuing to use the OraTest dye for selective retention into carcinoma cells.

Thank you.

Carcinoma and Carcinoma In Situ

Stephen Porter, Ph.D., M.D.

DR. PORTER: Good afternoon. My name is Stephen Porter. I am the Chairman of Oral Medicine at the Eastman in London and University College, London. I am medically and dentally qualified, and also hold a Ph.D.

[Slide.]

I have been asked to discuss the aspect which

seems to be of some concern regarding the difference of similarity between carcinoma in situ and oral squamous cell carcinoma.

I propose briefly with one slide to try and demonstrate or to demonstrate that there is no difference from a clinical viewpoint reaching a diagnosis histopathologically of oral carcinoma in situ and oral squamous cell carcinoma.

If one examines the literature, there is good evidence to suggest that oral carcinoma in situ always progresses to squamous cell carcinoma unless managed appropriately.

The histology of these lesions shows profound dysplasia. These lesions, if left, simply invade into the underlying tissues, and, hence, are squamous cell carcinoma. If one examines seven studies, the progression of patients with oral epithelial dysplasia, up to 39 percent of patients with lesions that have oral epithelial dysplasia show a progression to squamous cell carcinoma.

It was those lesions that had severe dysplasia or carcinoma in situ which showed progression.

If one examines the opposite, whether there is regression of carcinoma in situ, there is no evidence to support this notion with regards to the mouth. Certainly, lesions that are mild to moderate oral epithelial dysplasia

will sometimes show regression. For example, 16 percent of one study showed some degree of regression. But with carcinoma in situ, regression has not been recorded in the mouth. Thus, there is clear evidence to suggest that carcinoma in situ does not regress, but progresses to squamous cell carcinoma unless managed appropriately.

If one examines the risk factors for carcinoma in situ and squamous cell carcinoma, they are the same. Recent studies, for example, in the United Kingdom and elsewhere, show that the greatest risk factor for oral epithelial dysplasia, and hence carcinoma in situ, is tobacco.

Alcohol is another risk factor, and clearly alcohol and tobacco have a synergistic action, but they both give rise initially to oral epithelial dysplasia, then carcinoma in situ, and if not managed, squamous cell carcinoma.

It has been suggested that other factors may be important in the etiology of carcinoma in situ. There are not really any good studies to suggest anything other than tobacco and alcohol.

If one considers the molecular events taking place within carcinogenesis of the mouth, there is clear evidence to suggest that putative tumor suppressor genes may exist, and this, of course, is similar to that of malignancies of the lung, prostate, colon, and many other sites.

With regard to squamous cell carcinoma, at least three sort of hot areas are suggested, 3p, 9p, and 17p. These same sites have also been found to show loss of putative tumor suppressor genes when one examines oral epithelial dysplasia.

More importantly, when one examines carcinoma in situ, you find the exact same changes and the exact same frequency of these changes as you do in oral squamous cell carcinoma. So, not only do the patients have the same risk factors as squamous cell carcinoma, the lesions have the same molecular banks taking place, they are identical.

Oral carcinoma in situ should not be confused with carcinoma in situ, for example, of the female cervix, whereas, are linked with human papillomavirus is suggested or is demonstrated with the latter, this is not the case with carcinoma in situ in the mouth.

This is also demonstrated by the fact that if one examines persons with profound immunosuppression, you may see a raised frequency of co-malignancy, but you do not see this taking place with regards to oral malignancy, so viral etiology is not demonstrated, and again the molecular links are dissimilar between the mouth and the cervix. They should not be managed in the same fashion.

Lastly, carcinoma in situ presents clinically often as ill-defined red patches, sometimes termed

erythroplakia or leukoplakia type lesions, which are white patches of unknown cause. These sometimes are small, they are not ulcerated, and they are difficult to sometimes diagnose, particularly in an untrained eye.

Anything that could perhaps heighten the awareness of these lesions will be of some benefit, and to date, toluidine blue appears to be one of the few agents around that might do this.

The management of carcinoma in situ worldwide seems to be, and indeed is, the same as early oral squamous cell carcinoma. The difference is that carcinoma in situ is relatively straightforward to manage, whereas, oral squamous cell carcinoma is much more problematic.

As a result, the morbidity and even the mortality associated with carcinoma in situ, if managed appropriately, is strikingly different than that of squamous cell carcinoma.

So, to summarize, carcinoma in situ is managed by appropriate specialists in the same way as oral squamous cell carcinoma. If it is not managed appropriately, it will become a tumor. It has the same molecular events as oral squamous cell carcinoma, and it has the same risk factors.

Hence, when one demonstrates carcinoma in situ in a sample that has stained positively with toluidine blue, we manage it like a tumor.

OraTest as a Diagnostic Adjunct

Roy S. Feldman, D.D.S., D.M.Sc

DR. FELDMAN: Ladies and gentlemen, thank you for the opportunity to review the clinical data collected by my hospital and assembled by Zila as part of Study No. 44-389.

Let me put discussions this afternoon in a clinical perspective. I am Roy Feldman. My job is Chief of Dental Service at VA Medical Center, Philadelphia, and I teach at the School of Dental Medicine at the University of Pennsylvania.

In the course of this, each year I train some 120 dentists, 28 dental hygienists, 10 residents, and 20 visiting international scholars, so I know what it is to talk after lunch, and I promise I will talk both loud and fast.

Let me also paraphrase the slogan that is used by a prominent men's company. "In our view, an educated clinician is our best examiner."

[Slide.]

I want to explain that the key, the clinical issue in all of this is diagnosis, and that we obtain by a tool, the biopsy. It matters little how many biopsies are required to establish the diagnosis, parallel to the number of radiographs required to diagnose a fractured tooth or caries.

If one is looking at a lesion as prominent as this, there is very little we need to understand why the teeth have migrated, why the tissue looks the way it does. What matters is the establishment of the diagnosis. I want to show you what I mean.

[Slide.]

We face lesions that present similar to this in the floor of the mouth. The exact nature of the lesion, a pedunculated, hard, non-motile mass elevated above the floor of the mouth is not a particularly difficult issue.

The question is from where to establish the biopsy to establish the diagnosis. Using the toluidine blue, we are allowed to gain visualization not only of the lesion itself, but the margins of the lesion that allow us to gain access to those tissues that may be pathologic and those tissues that may not be pathologic.

This is the gold standard. It's a starting point from which to describe how to train those clinicians.

[Slide.]

You see here a lesion on the right lateral border underneath the tongue of a patient whom I have been following for 14 months. When I first started following him, I saw a lesion here on the right lateral border of the tongue, and a month later it was gone.

Thirteen months after that, while I was following

an additional lesion in his mouth, I found this small cavitation, and the way we would deal with this in a clinical circumstance, training students, is I would ask somebody from the floor to come up and point out that lesion in his mouth.

[Slide.]

In this case, we have the toluidine blue stain that demonstrates a spider web appearance across this lateral border. The biopsy taken from the central portion of this revealed moderate dysplasia. Mark you again this is a lesion that was clinically apparent, as you saw at the previous slide, and that I either didn't observe for 13 months or the lesion had disappeared for the 13 months.

[Slide.]

I ask you to look at this one. I love the fact that I can take 20 hygienists and work with them for four months and have them come to the board after a period of even after lunch to demonstrate areas of dysplasia or changes in normal in this floor of the month.

On your righthand side, you see a white bleb in a surrounding red base. That lesion I found. I found the red lesion in the floor of the mouth in the central regions, but neither my chief resident, a DM DMD, nor myself, found the lesions on the righthand side.

Let me show you what they look like with the blue

stain.

[Slide.]

The lesion on the left, that had the prominent white spot, was diagnosed as severe dysplasia. The central erythematous lesions were diagnosed as severe dysplasia. But the lesion to the right, to your left, on the upper left, was the carcinoma in situ.

[Slide.]

That patient had the floor of his mouth surgically removed, a procedure known as stripping. That procedure alters all the landmarks that one looks at. So when you look at him here, seven months later, you have no idea where specifically are the landmarks that you saw before.

That central line that holds your tongue in place, that allows you to form words, allows you to speak, that has been obliterated and replaced by this large white scar that you see traveling horizontally across the photograph. Clinically, the floor of his mouth is altered, as well, and the nature of some of the coloration of the tissue is altered.

This is the scar across the center portion of his mouth, which changes the way you look at his mouth, and here are areas of inflammatory change. Look what happened here.

[Slide.]

Both areas were diagnosed as squamous cell

carcinoma. This is despite the fact that he had been observed for a six-month recall by the surgeons who had stripped him the month before.

Certainly, examiners may describe lesions encompassing mucosa beyond which that is delimited by stain, or lesions of differing borders from those stained because of inflammatory components.

These are high-risk patients. Their mouths don't look like what I hope your mouth looks like or my own, and cartographic discrepancies arise, and by that I mean identification of a lesion presenting with indistinct borders can be delineated in different areas on a mouth map by different examiners.

That is specifically the history of Patient 106 that you saw in the assembled data, and Zila recognized this problem and instructed PI's, such as myself, and our study coordinators to permit and demand a recording of one lesion, in one location, even if two examiners confused the landmark. It allowed for some communication by the study monitor to establish specific locations.

I think you may appreciate how easily this problem arises from the clinical slides. If urgency is biopsy is the clinical issue, protocol cannot drive biopsy sequence. Once lesions are clinically indicated for the diagnostic procedure, note you clinical latitude in this definition and

characterization of stain is permitted by protocol. This is neither a violation nor discrepancy for protocol.

Protocol in this study appreciated that clinical acumen is required to interpret clinical findings.

Let's look at Patient 424. This patient had salient lifestyle factors which featured prominently in his management. He persisted in smoking and in alcohol use despite his testimony to the contrary. He sought palliative pharmacological management for mouth pain, i.e., more drugs.

He traveled for more than five hours one way for his appointment, and consistent with his clinical description, he presented with bilateral necrosis of the jawbone. Can you imagine why he might refuse to have biopsy of those areas in which he felt pain.

Urgent biopsy in his case would have been the only ethical management issue, that the stain indicated active disease in spite of radiation-associated xerostomia, continued drying of the tissues from smoking and the alcohol use, abrasion from the exposed bone, and other trauma is indeed remarkable.

The clinicians would recognize a bilateral tongue lesion as inconsistent with manifestation of neoplasia is rudimentary. Finding of a midline lesion by stain alone is credited with advancing the therapeutic potential of cancer management. There is neither disregard for lesion

suspicious to any informed practitioner, nor is there favor of management of any lesion not identified by protocol.

There is, however, appreciation for early diagnosis of a life-threatening pathology. This is exactly what we need tolonium chloride to do. In a clinical study, the data that count are the data you get. If you don't see it, then, you don't get it.

What do we do with the data? We send them to pathologists. Standards of convention communication between surgeons and pathologists demand communication in order to establish a meaningful diagnosis.

That is the purpose of the exercise. Concealment of findings from a pathologist would question the ethical motivation of the submitting surgeon. This is standard procedure consistent with conventional clinical practice and compliant with protocol and my CRF are properly documented.

Any deviation from this in the case of Patient 133 would be unethical.

Clinically, this panel recognizes that one manages complex therapies for complicated patients. It is hoped that a single, simple, non-invasive and obviously visual diagnostic aid will be made available to train my students, comfort patients, and provide clinicians with a new edge on this sort of oral cancer management.

Thank you very much.

Clinical Experience and Biopsy Site Selection with OraTest

Joel Epstein, D.M.D., M.S.D.

DR. EPSTEIN: Thank you for the opportunity to be part of this session. I am Joel Epstein. I am at the BC Cancer Agency in Vancouver, Canada. I am head of Hospital Dentistry at Vancouver Hospital and the Division of Hospital Dentistry at the University of British Columbia. I am also a research associate professor at the University of Washington in Seattle in Oral Medicine.

[Slide.]

I was asked to not review really the material that you have seen, but to try to indicate some of the things that we have troubles with clinically, and where we feel that the value of an adjunct in diagnosis or site selection will be particularly helpful.

I did want to mention one thing about the study that was referred to by Dr. Green at his introduction, and that is that this was a clinical protocol that we had instituted at the British Columbia Cancer Agency based on previous studies, one of which was our own, using toluidine blue as a guide to diagnostic testing and evaluation of patients.

This was a series of consecutive patients that were referred to me specifically based upon the presence of

oral tissue change. Now, this is different than the current IND study, which is an evaluation of previous head and neck cancer patients without necessarily there being previous or obvious oral soft tissue pathosis or tissue change.

I should also mention that the previous study that was mentioned, that we published in 1997, was not supported by funding from Zila.

[Slide.]

What I would like to do is then point out and just provide a couple of examples of instances or conditions under which a diagnostic aid is going to be helpful in evaluating oral soft tissue disease, and I have one particular clinical case that we have run across recently that I think might be of interest.

As well as just the difficulty in assessing oral soft tissue, familiarity with normal versus abnormal, access to good lighting, and evaluation of patients in a good, thorough sense, even in that setting, lesions are missed, but in particular, if we are dealing with other conditions, such as patients that have few and minor mucosal changes, patients with multiple sites of oral lesions whether they be white, whether they be irregular white, red and white, or just red, make assessment difficult.

The difficulty is also, as I will show in one of the cases that I will show in a few slides, one based on red

lesions either representing inflammation or, in fact, being truly carcinoma in situ or invasive carcinoma, and that is the erythroplakia or erythroleukoplakia.

Lichenoid mucosal changes, which are common dermatological oral findings, can sometimes be difficult to assess. There may be field changes throughout the mouth in patients who have dysplasia or malignancy, and while we might identify clinically the obvious lesion, we may miss many other sites that are currently involved that require perhaps a change in therapy and approach to management.

Patients may have multiple concurrent or synchronous malignancies in the upper aerodigestive tract, again affecting outcome and choice of therapy, and then, of course, patients who have had a previous malignancy may have recurrent disease, persistent disease, or again new primaries.

[Slide.]

The assessment of patients who have had medical therapies may be also very difficult and confusing to people who don't see patients on a regular basis in this setting, and particularly those who have had previous oropharyngeal cancer and therapy may have changes due to radiation therapy, surgery, that complicate both the assessment and cause some concern on the part of clinicians with respect to the frequency of biopsy of tissue change because patients

who have had head and neck radiation therapy have very delayed healing potential and therefore we may be delayed in our assessment that we must biopsy a mucosal lesion based upon our concern that healing may be delayed or not occur, leading to exposure of bone and necrosis, for example.

So, those following radiation therapy may be much more difficult to assess, and our decision to proceed with biopsy may be delayed unless it is facilitated by additional clinical findings.

The one case that I am going to highlight at this point is one due to immunosuppression, and as medical therapies and diseases causing immunosuppression increase, we will see more of these, and, for example, patients following bone marrow transplantation may have an inflammatory, almost immune-based disorder termed graft versus host disease, that may have oral manifestations.

Patients following organ transplant also in this group may be immunosuppressed, and certainly patients that are on prednisone and other immunosuppressive diseases for other conditions like rheumatoid arthritis may also be in this group of patients.

[Slide.]

So, what I want to show you is two cases. The first is a case of patient following cancer therapy for a T1NO squamous cell carcinoma in this area of the tongue, and

you can see both the effects of surgery and the effects of radiation in this side.

There is a change in contour, there is a change in function. If you could hear the patient, you might notice a change in speech and ability to chew foods the way they used to. There is late radiation changes with vascular changes and scarring beneath the mucosa.

Now, this site, in better light actually, there is a very small, diffuse white plaque that looks more superficial than the whiteness that is probably due to fibrosis beneath the mucosa.

[Slide.]

This wasn't the area that we were concerned about, it was this side, on the opposite side of the tongue, which based upon the radiation therapy, which was external beam, there were mucosal changes on the other side that we thought could either represent later radiation effects or again another lesion.

The question would be, as shown in previous slides, is if you are going to sample this, first of all, knowing that healing may be delayed is one issue, but the other is where do you sample it.

[Slide.]

This particular case was guided by the dye uptake, and you can see that probably the best site may be here or

here, one in the red, one mixed in the red and white area, and this was another invasive cancer.

[Slide.]

The next case I want to show -- and I have a brief history available if you want the copy -- it is a case of a patient with chronic myelogenous leukemia diagnosed in 1992, treated with marrow transplant in 1993, who developed graft versus host disease with successful management.

For 12 months, he had GI symptoms. For 24 months, there were skin lesions visible. Throughout that time, there were minor, basically insignificant oral changes essentially limited to the left lateral tongue, and I will show you what it looked like by the time we saw him.

He was off all immunosuppressives for some three and one-half years prior to us seeing him, and he was seen at five a one-half years following transplant. At that time, he was referred because of increasing discomfort on the left tongue.

Back in June of 1998 -- and we saw him in October 1998 -- he was seen by the Department of Otolaryngology, and they identified changes on the left tongue that led to biopsy, which was not guided by toluidine blue, and was diagnosed as hyperkeratosis, and it was put down to local trauma or irritation, not to GVHD, by the way.

But because of increasing sensitivity and redness,

he was put on topical steroids and continue that through the summer until we saw him in October. At that time, he had lip lesions that looked like this, and I don't know how well you can see this throughout the room, but there is sort of lichenoid patches and areas of striations that are faintly visible, patchy white and red areas across the lip.

[Slide.]

And very minor changes that I don't think are going to show up on this slide in this light, on this side of the cheek and the opposite cheek was similar.

[Slide.]

The significant clinical change was on this side of the tongue. Now, this is an example of an area that is red in the back, patchy and blotchy white up front, and the issue would then be is this inflammatory or is it potentially dysplastic or neoplastic.

He had been on topical steroids for several months, so at that point we decided a repeat biopsy was indicated despite the previous benign results.

[Slide.]

To help guide our tissue sampling, we applied the toluidine blue. Now, on this slide, I will point it out, and you will probably see it in this light, in the center of the red area, not all of it, there was this patchy blue distribution. There is really no uptake. There is very

little retention in this site except in the crevices where the dye may accumulate on the surface, not in the cells.

[Slide.]

In this area, though, more anteriorly, you start to see some uptake there and there. Now, what I am going to show you are the sites in which we did the biopsy because we photographed this at the time, and I will tell you the techniques we used, so you can understand what is what.

[Slide.]

This is a punch biopsy technique in this site, this site, and a wedge biopsy technique at this site with a suture in place.

You can see that we sampled the central portion of that red area where the blue was retained, an area where there really wasn't any retention, but was white and somewhat irregular, causing a clinical appearance that might be suspicious or a nodular leukoplakia in essence, and this site where there was moderate retention.

Let me tell you what the biopsy results showed. This site was mild dysplasia, this site moderate dysplasia, and this site was carcinoma with microinvasion.

So, we believe that this is a useful adjunct in difficult clinical settings including in environments where people are seeing oncology-based cases on a daily basis. So, we have continued to use this as an adjunct in our

clinical examination.

Thank you.

Concluding Remarks

Ralph Green, D.D.S.

DR. GREEN: Thank you. That completes our presentation. I watched yesterday as the panel went through this discussion of the glioma and the astrocytoma, and talked about survival rates and quality of life.

I think that if you just take a look at the SEER data and take a look at the CDC data that essentially talks about changing patients, getting earlier diagnoses, moving more patients from Stage I and Stage II, where we have a cure rate and we have 80 percent survival rate as opposed to Stage III and Stage IV, which is much more difficult, then, you can see some of the needs for this particular product.

I also need to remind you again that this is an adjunct therapy for a subset of our screening claim. As we see it, it is clear that there is no reason to discount the carcinoma in situ and that the study shows that the staining that does identify sites in a way that makes the biopsy an informed biopsy, and this data goes to support the selection approval.

In the FDA review of the data, there exists some differences of interpretation of the clinical information. The principal investigators are here. They support the

company's classifications of these lesions as non-apparent, and they would be willing to discuss any particular case that you feel is appropriate.

We, as a company, have made our first visit to the Oncology Division, and we are prepared to continue to do clinical research and chemical research as needed.

I would just like to remind the panel that this is the week that marks the 35th anniversary of the first Surgeon General's Report on Smoking. In those 35 years, some 300,000 Americans have died from oral cancer. In those 35 years, the five-year survival rate of oral cancer has been stagnant. OraTest may help the nation's health care providers as you have seen here today, particularly dentists and primary physicians, dramatically improve this patient outcome.

Thank you. I have noticed that some of the speakers have arrived.

DR. DUTCHER: All right.

Is Mr. Robinson here? Could you come up to the podium and just give your name and any affiliation with the sponsor, please.

Open Public Hearing

MR. ROBINSON: My name is Alan Robinson. I have no financial affiliation from the sponsor in terms of payment, and so forth. I have purchased shares in Zila over

the last six to eight weeks, and when I saw the price drop to 4 1/3, I started saying it didn't make any sense to me.

I am here because I am a cancer survivor. If you don't have my statement, I have copies here to pass out. I apologize. I didn't know you moved it up. I do work in postal consulting, so this isn't very new to me. I am familiar with testimony.

I am here and I appreciate having the opportunity to talk this afternoon because I am a survivor, and specifically tongue cancer, and if you want to see a picture of my tumor, I brought it with me.

What is unusual about my story is I was treated at George Washington University through intra-arterial chemotherapy followed by radiation. I still have my tongue, there was no surgery, and the cancer is gone.

I was lucky. Most people aren't so lucky. At almost any hospital in the United States, my tongue would have been removed, in all likelihood I would be permanently disabled, and I could not have clearly articulated the oral testimony today.

I am here not to tell that story, but to testify on behalf of Zila. I am here today representing, as I said, no one but myself. I am going to read part of the statement and leave the rest for you.

I am here testifying for five reasons.

First, as a person who now has a one in five chance of reoccurrence of cancer. That is what my doctor is saying. I would personally benefit from the availability of OraTest, and it would increase the likelihood of early detection of a new cancer during either my triennial dental visits or otolaryngological follow-ups.

Second, I am personally impressed by the research. To me, it looks like a no-brainer, and given the option, I would choose using OraTest every time. I believe that others in my situation would do the same.

Third, I personally experienced the misdiagnosis of cancer. My doctor first saw me in July of 1995 for a sore on my tongue and coincidentally recommended that I use Zilactin to treat the sore and then go see a dentist.

I was not officially diagnosed until mid-September when I finally saw a dentist and I had a Stage IV tumor. My experience of delayed diagnosis is not uncommon. If OraTest had been available to my doctor, then, a diagnosis could have been made three months earlier.

I am my doctor's only oral cancer patient, so her experience in looking at tumors is extremely limited.

Fourth, I understand the devastation or oral cancer and believe that OraTest could significantly reduce that devastation. In the course of my treatment, I came across a man in his mid-thirties with a 5-year-old daughter

who had a cancer similar to mine. He went through at treatment of intra-arterial chemotherapy and radiation similar to mine that unfortunately did not successfully eradicate the cancer.

He has a whole series of biopsies that eventually found another tumor, and he had both his tongue and voice box removed. While OraTest would not have prevented the cancer, regular testing for cancer may have found it much earlier and permitted a much less destructive cure.

Fifth, oral and head and neck cancer patients feel like orphans in the medical community. Today, oral and head and neck cancers affect 50,000 Americans annually. This is more than the number that are affected by leukemia, melanoma and cancers of the brain, liver, kidney, thyroid, stomach, ovary, or cervix.

Yet, at this point, there is no research foundation for cancers in this region, no celebrity spokesman, and public knowledge of early warning signals or risk factors of head and neck cancers is significantly less than for many other cancers. Even drugs such as Salagen, that can alleviate dry mouth suffered by oral cancer survivors used the "orphan drug" approval process.

The "orphaning" of the oral and head and neck cancer community makes being a patient and then a survivor much more difficult. Throughout my treatment, I was angry

that so few had access to treatment options like mine. Following treatment, I could not understand why so little was known about monitoring and alleviating dry mouth and other side effects of treatment. My difficulty was intensified by the low interest by the general media in my disease.

During the entire period since my diagnosis, I cannot recall a single news story on new tests and/or treatments for oral and head and neck cancer in either local or national publications. Even the remarkable results of preliminary findings on OraTest and intra-arterial chemotherapy have failed to receive attention. This is despite my attempts to provide information to the health editors of all Washington area television stations, the Wall Street Journal, New York Times, and the Washington Post about both my treatment and the early clinical results of OraTest.

I believe that the "orphaning" of this cancer is due to the difficulty survivors have in going public with what they have suffered through and the results of treatment. Cancers in this region have affected many in the public eye who could have increased awareness of this disease.

Survivors now include Brett Butler of the Los Angeles Dodgers, former Speaker Jim Wright, actors Jack

Klugman and Gary Busey, and comedian Alan King. For many survivors, surgery to remove the cancer also removed part of their face or their larynx. Survivors face incredible embarrassment over the physical change that cannot be hidden by clothes. Furthermore, changes in the mouth and throat makes talking and eating more difficult, if not impossible, and public appearances may become almost too much to bear. As I have survived with the capability to speak, I am here for those who cannot.

The remainder of my testimony is material from the public record, and I will let you read it on your own, but I really do appreciate this opportunity to talk, and if there are any questions, I will be glad to answer.

DR. DUTCHER: Thank you very much.

MR. ROBINSON: I don't know if it is appropriate to pass out my pictures.

This is the tumor when it was diagnosed, and the last one is the picture after five treatments of chemotherapy. So, it is my chance to promote that, as well, but it is pretty remarkable to think that a doctor missed this, and that's the scary part.

DR. DUTCHER: Thank you very much. We appreciate your coming.

Are either Mr. Kanakis or Mr. Corbin here? We will start with Mr. Ted Kanakis.

MR. KANAKIS: I am Ted Kanakis. I am just a basic citizen. I have no financial connection with Zila itself other than about a year and a half ago I did buy -- I found this company through some research, and I kind of bought -- I own a total of 775 shares, which is in my IRA account, which is not going to make me a rich man depending on whatever happens here today. However, I also own stock in Starbucks and Ben and Jerry's. I am one of those people that try to invest in companies that I believe do good things aside from making profits, and I believe from what I have heard today that Zila does that.

I speak to you today, not as an expert on oral cancer or the political merits of OraTest, but merely as a concerned citizen. I am a defense contractor and a former Army officer. My interest in this meeting relates to my fear and contempt for all cancers, and my desire to see it never affect a friend or relative again, and my belief that medical science should provide us as many alternatives as possible in our society's collective fight against the cancer monster.

Although I lost two grandmothers to cancer, it was not oral cancer. Their cancers were related to internal organs. However, I am now 40 years old, and I still vividly remember my first introductory awareness to cancer as a disease when a second grader.

That awareness came about when a friend of my teacher's came to school to warn us on the dangers of smoking and cancer. This man had oral cancer and was soon to die. He had determined to use his remaining time in life in an attempt to keep others from his fate. He was then horribly disfigured and spoke with great difficulty in a scratchy voice.

What I remember most was his saying that I didn't even know that I had it until I lost two teeth eating scrambled eggs. I went on to grow up like most kids in America except for one respect. I never smoke cigarettes. Although I tried a few in my teens and twenties, I always remembered that man and his scrambled eggs, and consequently avoided that means of trying to fit in.

While in the Army, I knew many fine soldiers who did smoke and many others dipped smokeless tobacco. They were great Americans with whom I spent many hundreds of days and nights guarding freedom's frontiers in conditions that were primitive and in places that none of you would really choose to visit.

After the Army, I came to live in this area as a civilian and have met a great number of people. First, my boss, with a big smile, hired me simply because he wanted to give a vet a break; to my sister-in-law, a single mother whose husband ran off, one of the most caring mothers I

know, and several other friends that I have now with whom I do charity work on a regular basis. Did I mention that each of these type of people use tobacco?

We all know here that oral cancer affects primarily smokers and drinkers. Some may reason that they bring it on themselves and therefore they deserve what they get. I believe that is a cruel and ignorant viewpoint.

We all know that oral cancer is only the 8th most common form of cancer affecting only 30 some-odd thousand Americans per year, killing only 8,000-plus Americans annually, only about one an hour, but it is my hope that each of you on this panel see individuals among America's 62 million tobacco users and as great a number of drinkers.

In your own lives, each of you probably knows and cares for people who smoke or drink, just as I do, whether or not you personally choose to indulge. Finally, who can really say how many others never smoked because of that man that I met in second grade with oral cancer, how many lives did he save?

I wonder if it wouldn't somehow repay his compassion almost 30 years later if we give the American public a product that might provide an earlier, more survivable diagnosis of oral cancer. Give them OraTest.

Thank you.

DR. DUTCHER: Thank you.

Mr. Corbin.

DR. CORBIN: Good afternoon. My name is Dr. Stephen Corbin. I am the Vice President for Professional Development and Institutional Advancement at Oral Health America.

Oral Health America is a national nonprofit foundation that has existed since 1955. We are based in Chicago. Simply stated, our job is to try to improve and protect the oral health and the general health of the American public. We do that through educational programs, programs that promote access to oral health care by the underserved, and innovative projects that relate to dental education and dental research.

In terms of financial interests, I must state that my participation this afternoon is on behalf of Oral Health America. Unfortunately, I have never received any compensation or considerations from Zila or been promised any considerations like that to appear at this meeting or any other place. I have never owned stock in Zila or any of its subsidiaries. In fact, Oral Health America employees are not permitted to own stock in individual companies that form the constituency base with which Oral Health America works.

We are a charitable organization. We do rely to a great extent on contributions made by individuals and

companies, and contracts and grants that we receive from other organizations. Zila did provide us a modest contribution in 1998, one of several thousand entities that provided us some resources to carry out our charitable programs, however, Oral Health America and its employees have never specifically promoted a product manufactured by Zila or any of its programs or activities.

Dr. Ralph Green, who is the general manager of OraTest USA, is a non-paid volunteer member of OHA's 20-member board. I don't know if I broke the record for disclaimers, but hopefully, I have some left to make some relevant comments.

I want to focus my comments around dental practice and public health, which really are my strongest areas of expertise. I have provided written comments to the panel in advance, which I assume have been distributed.

I have got a slightly updated and improved version that I will leave with you today, but it shouldn't substantially impact the comments that I am making. I also provided some examples of educational materials that Oral Health America produces, and I brought some additional ones today.

The National Spit Tobacco Education Program is the most visible program of Oral Health America. It has been in existence for three years. The purpose of this program is

to keep America's youth from using spit tobacco. Why? Because spit tobacco causes all kinds of health problems predominantly in the oral cavity, and one of them is cancer and precancer.

Thus, we have a very high interest in any product or any program or any approach that can help reduce mortality and morbidity from oral cancer.

In the U.S. today, as you are well aware, there is over 30,000 cases of oral and pharyngeal cancer, over 8,000 deaths, and there are many, many survivors of oral cancer that are highly disfigured and suffer all kinds of problems which I am sure you are familiar with.

The five-year survival rate of oropharyngeal cancer has not improved markedly over the last several years, still around 50 percent. There are many factors that contribute to these statistics, and we don't have time to go over them today. Obviously, alcohol and tobacco have been mentioned.

One of my big problems is how do I get dentists to do the right thing, and how do I get dentists to be effective in early diagnosis, counseling, and monitoring of patients that have had oral cancer regardless of the stage at which it has been diagnosed.

It is of concern to me that most oral cancers and precancers obviously start out at a very subtle, difficult

to see, let along diagnose, stage. In fact, 80 percent of asymptomatic erythroblastic lesions were found to be less than 2 centimeters in diameter, and almost 40 percent were 1 centimeter or less.

Given the saliva, the lighting problems, tissues moving around, the differential colors in the oral cavity, this creates a great problem surely for general dental practitioners, but also, as we have heard, probably from people that have a little bit more sophisticated experience, clinical experience and training.

Beyond this there are system factors, because dental students don't learn that much about oral cancer and diagnosing precancerous and cancerous lesions in school, and they get very little direct experience with biopsy and following up patients, nor do they get much experience in talking to patients about oral lesions and tobacco and alcohol, and how you get off of these products and their relationship to oral cancers and other health challenges.

This is where OraTest comes in. Only a small percentage of dental clinicians have used toluidine blue. It has been around for decades. Those that were more ambitious and had some experience with it, the graduate programs know how to mix it up and use it, and get it on the lesion rather than all over their lab coats and their pants and the floor, but by and large, dentists do not use this as

part of their armamentarium. This is a problem.

Mashberg has identified the underutilization of toluidine blue as a diagnostic adjunct as a principal reason that nonpalpable, nonulcerated, minimally elevated asymptomatic oral cancers do not get diagnosed at early stages.

In fact, 80 percent of oral cancers are not diagnosed at early stages. This is a big problem, and this is why the five-year survival rate has not changed much.

Dentists like to work with protocols. I think if a product like this were available to dentists in a unit dose that could be conveniently used with patients, that this would enhance their utilization of these diagnostic techniques.

We also know that dentists do not routinely provide comprehensive oral exams for patients that return every year. This is another problem, and I think this product could help influence the protocol implementation and individual dental practices.

The fact that commercially available toluidine blue is marked "Not for human use," and that you need to get it from laboratory supply houses or pharmacies, I think is another practical constraint to getting dentists to use this type of a diagnostic procedure.

In the United States, every year there are over

100 million visits to dentists by patients who use tobacco. Clearly, there is a large universe of potential patients there, and we feel like those patients that are tobacco users, particularly those that have a history of oral lesions, would be prime candidates, those older patients, those that use alcohol, those that are in the highest risk group.

As I said, the NSTEP program is a major undertaking of ours for the last three years. We expect to expand our programming in the next several years, both on spit tobacco, general tobacco, and involving the dental clinician. There are over 400,000 people work in dentistry clinically, and tobacco cessation, tobacco education, and early diagnosis and treatment of oral cancers.

We see this as a critical continuum. We also believe that beyond the ability to diagnose and characterize oral lesions clinically, the toluidine blue stain is an excellent patient education tool, particularly when you combine it with some of the newer technologies available today like intraoral imaging where the patient can actually look on a television screen and see in pretty good quality images blown-up portions of their mouth, and in this case, whether it is a cancer or not, what a fabulous educational adjunct for getting people scared enough or smart enough to try to stop using tobacco.

With that, I will end my comments and if later on there are any questions, I would be happy to field those, and I will leave the extra educational materials and the revised comments with the Chair.

DR. DUTCHER: Thank you, and thank you to all of the speakers for letting us work around the time constraints and scheduling.

We are going to proceed now with questions from the committee for the sponsor.

Dr. Johnson.

Questions from the Committee

DR. D. JOHNSON: As a first issue in clinical trials, I am always bothered by the fact that the trial is not followed as planned. The study really boils down to 17 lesions. The study was designed, as I understand it, to accrue to a total of 160-some lesions.

I am also extremely troubled by a study that does an unplanned interim analysis and then uses those data to make a point. I think before other questions about the study and the information are addressed, the sponsors have to deal with that.

DR. GREEN: There is no question we would prefer not to be here with 17 patients. I think that in my opening remarks, in terms of the regulatory history that has brought us here today, we have defined that, what we had anticipated

as being a paper NDA that was submitted, and as the device was submitted in 1991, and the paper NDA that we thought was going to be approved, was, in fact, documents that were presented in 1996.

We also, at the NDA that we presented, we used as our pivotal studies Dr. Mashberg's study, and Dr. Mashberg's study was at that time considered to be the gold standard, and the gold standard at that time, and I think even the gold standard today, as mentioned in the FDA reviews, is that every lesion needs to be biopsied.

Dr. Mashberg biopsied every lesion. His was the gold standard, and that was rejected by the Oncology group. We, at this point in time, took a look at the only data that we had available, which was an IND data for screening going forward, and at the point in time where we entered into this discussion with the FDA, we then took a look at that date, which was October the 7th, and looked at the enrollees into the protocol from the beginning of time to October the 7th, and used that as interim data.

At that point in time, we did not have any other data. Today, the only thing that we have to present to you is a subset of our initial clinical, which was for the screening. There is no other data to present. We wish we had more. We wish we had some studies that -- as you know, doing oral studies in oral cancer is not a very easy thing

to do, number one, nor very economic thing to do.

We just brought to you the best information that we could at this time.

DR. D. JOHNSON: I would like to then address some issues that, unfortunately, you failed to address in your presentation. There are some very clear-cut discrepancies between the interpretations of the pathology reports, your company, and by the FDA reviewers, some of which seem unequivocal in my mind in reading the pathology reports, namely, that visual lesions were, in fact, seen based on the information presented to the pathologists, i.e., ulcerated lesion biopsy. That is not an unseen lesion, and yet it was characterized as such.

DR. GREEN: I would like to have Dr. Dolor discuss that.

DR. DOLOR: I think I will start with being the first investigator to talk about some of the discrepancies in the FDA report since my site was responsible for four of those.

For our path reports, I will answer that question first. It is true that the visual examination did not notice a lesion. For example, in Patient 199, he had a lower lip lesion that was missed on the first visual exam at the first visit, but was seen by OraTest that visit, and then the patient came back for a second visit, and the

lesion was then seen visibly, as well as with OraTest.

What we put on the path report was the results of the OraTest staining, and that is what we used to give our pathologists locally. Otherwise, we wouldn't know, you know, based on visual exam, what to put down on the oral report. I think it is unethical to give our local pathologists no clinical information to make the diagnosis, and then, second of all, the slides were forwarded to the central pathology lab without any clinical history.

There were maybe some numberings on the slide, the sample numbers from the site, you know, Sample 98 something, something, but nothing was marked on there whether it was a T10, T13 lesion. So, the independent evaluation by the central lab was blinded, and not by the local lab. So, in Patient 199 --

DR. D. JOHNSON: Let me interrupt you just one second. I apologize. The question isn't the interpretation of the biopsy itself. The interpretation, the issue is was, in fact, a lesion visualized and biopsied when, in fact, it was reported as a lesion identified only by OraTest. That is the issue.

DR. DOLOR: Okay.

DR. D. JOHNSON: And a central review cannot tell that. They can only confirm a pathologic diagnosis.

DR. DOLOR: I reviewed the case report forms, page

by page, after receiving this FDA reviewer's report, and I can tell you that the visual examination for Patient 199, for that first exam, they missed the lesion. They did not see it visually. It was picked up by dye. It was only seen on the second examination, and so for Zila, they count that as a lesion that was not seen visually because, on the first examination, it was not clinically apparent.

For -- let's see what other patients were brought up -- for Patient 321, the visual exam showed lymphadenopathy, but no oral lesions were identified, and so the FDA reviewer infers from the presence of lymphadenopathy, and the clinical history and the pathology report, that the lesion should have been seen visually, however, this was not the case. The lesion was only found by OraTest alone in our records.

DR. D. JOHNSON: Let me address that particular case. I didn't intend to do it, but since you brought it up. In a patient with a history of head and neck cancer who presents with lymphadenopathy, even without a visual lesion, there is some suspicion that there may be recurrent disease, so finding a lesion in the mouth is not necessarily going to be beneficial if one can, in fact, biopsy the lymph node or needle the lymph node. I mean there is no benefit in my mind in that situation to have found an "occult" lesion within the mouth at that juncture. It defeated the purpose

of the early detection.

DR. DOLOR: First of all, let's presume that there was no OraTest, and this patient went into examination, and we found only lymphadenopathy. That means that as a clinician, you would have ordered a fine needle aspirate of that lymph node, and still not known where the primary was located until you maybe did a neck CT and saw something at the -- I think it was over in the --

DR. D. JOHNSON: So, you are telling me an OraTest will displace the neck CT scan?

DR. DOLOR: Well, I am telling you the OraTest will help you identify the primary without having to do an FNA of the lymph node, and as we know, the drainage for the anterior cervical chain does oropharynx, as well as some of the glottic structures, and so you wouldn't have known whether it was an oral primary or a glottic primary, I think, even if you just knew that there was lymphadenopathy present.

I am sorry, go ahead, sir.

DR. D. JOHNSON: I don't think I have any other questions. I was going to ask another question, but I don't think I need to.

I will just ask one other issue, and that is, a comment was made early on about no one ever dies from a false positive. Let me assure you that that is incorrect.

And you also say that when I look at the OraTest material, and I looked at the slides that were shown to me, and I just heard from one of the public speakers that he is the "only" patient that his physician follows, I have real reservations about the ability of an inexperienced physician to use this test, where, in fact, it may further increase the false positive, and I can assure you that false positive studies do, in fact, lead to other studies that, in fact, can have considerable consequences to patients.

So, I would like to know from the manufacturers here what kind of experience do they really have in a setting other than a VA where there is a high incidence of head and neck cancers, what kind of information do we have about screening, which is what really we are looking at in this situation.

DR. GREEN: We do have some other information, as a matter of fact, in a July-August face-to-face meeting with the Oncology group. We presented with not only Dr. Joel Epstein, but also Dr. John Wright, who is the President of the American Association of Oral Pathologists, also on teleconference at that point in time was an oral maxillofacial surgeon from the Island of Jersey, and the OraScreen, the name of it is on the Island of Jersey, he gave a two-year clinical experience that he had that, in fact, there were fewer false positives, and by utilizing the

14-day follow-up, it eliminated a lot of the biopsies that he was getting clinically because the clinician was now alerted to the fact that there was a 14-day period, and on the second step of the OraTest or the NIH protocol, that that would eliminate a lot of the traumatic lesions that he was getting to biopsy whether he liked it or not.

So, his clinical experience, and that clinical experience has been also replicated, although not published throughout the rest of the U.K., seems to be a reduction in the biopsies and a reduction of the false -- at this point in time, a reduction of the false positives simply by waiting that 14-day period.

I don't have any other clinical data to present to support that other than anecdotal information.

DR. DUTCHER: Dr. Forestiere.

DR. FORESTIERE: I certainly agree with the issues that Dr. Johnson has raised, in particular this last one concerning quality control issues.

I wanted to ask a question regarding the expertise of the individuals at the sites and the consistency of follow-up by the same individual at those sites for the serial visual examinations.

Certainly, there is a learning curve to deciding what to biopsy and what is really suspicious for biopsy. I think there would certainly be a learning curve for

interpreting the toluidine dye, as well. So, just picking up on that last point.

DR. GREEN: I am going to ask Dr. Feldman to chime in here, but that is, in fact, something that we have, as a company, in the setting we are in, we are dealing with specialists and we are dealing with oncologists because that is the subset of the screening population that allowed us economically to do the study that we have presented here today and the screening study that is going forward.

We realize, and we honestly think, as Dr. Corbin alluded, and one of the things that Dr. Corbin did not say was that he was a formed chief dental officer in the United States. We think there is an opportunity for education, not only oral cancer, but also toluidine blue, and we think that people like Dr. Feldman can address that issue.

Dr. Feldman.

DR. FELDMAN: These really are important concerns in any clinical research trial, and I appreciate exactly what you have pointed out. For example, we made an error in a case report form in my site, and recorded that both first and second exams had been done by the same person on one of the protocol sheets. The next protocol sheet where the exam was actually recorded showed two different names and there were two different signatures.

So, we had a problem that was a case report form

error, discrepancy in terms of nomenclature for the names of the people, but there were two people who had accomplished the procedure. That is something that the protocol has been able to follow through. That, you can define.

What you can't define is exactly as you raised the question, what sort of learning curve is there, and how will this work in the hand of the uninitiated. That is not something that this study purports to describe. What it does purport to describe is 12 centers, and from 12 centers, this same sorts of observation or at least there are in 11 of the centers.

So, yes, the nature of the learning curve is an important criteria. I thought that one could almost characterize toluidine blue as Arthur Mashberg in a bottle many years ago. It was Arthur's ability to recognize the lesions whether or not they were stained. Well, I didn't have that ability.

What you raise are very interesting questions as to how this would be used both as after it became a training aid, a teaching aid, as to how it would be used by people who are not as well experienced with it.

We tend to feel that the fact that it would show something is blue would be a great help.

DR. FORESTIERE: What was the quality control at the sites to make sure that there was consistency, and in

terms of your case report forms, how many situations were there where there wasn't consistency in the same examiner, and how were those handled, then, in the interpretation of the data?

DR. FELDMAN: You are asking a lot of questions here. I think I can address some of them. I think I am the only one who had one person sign his name twice on one of the sheets -- that didn't sign his name, had the study coordinator put in one person's name twice on two lines. I think we are the only people who did that. That was just once, and that is just an error.

The other part of your question comes about to when individuals would follow cases. Presumably, a visual examiner should repeat the visual exam the second time around and presumably, a stain examiner should repeat the stain exam the second time around. One should not cross these two, because there could be some memory that the stain examiner could bring to his test the second time around.

I don't have personal experience, but I think that happened only once -- and was it one of your patients, Joel? At least once. It happened rarely. So, for the most part, we did manage to adhere across the 12 sites to having no corruption between examiners for the oral exam, the visual exam, and the stain exam, which I think is the greatest source of bias that you can introduce.

I think that is the worst case scenario for that, isn't it?

DR. FORESTIERE: It certainly would introduce bias.

DR. FELDMAN: Presumably. It would certainly introduce bias, yes.

DR. FORESTIERE: And there wasn't communication between these two? I mean nobody knew what the --

DR. FELDMAN: I can't speak for everybody's center, but she throws me out of the room. Real simple. She throws me out of the room, and the next fellow comes in, and we do not discuss the case.

The only trouble we had was the identification of the site of the lesion on the mouth map, the cartographic identification, and that came about through a patient wherein it looked like there were two separate lesions, and they were really in the same place.

Zila saw that and instructed our study monitors to attempt to rectify this, so that a 2-millimeter discrepancy in location wouldn't come about as if it were two different sites, and, in fact, what might be the same site if there was but one lesion, and I called it on the lateral border of the tongue, and the next fellow in called it underneath the tongue on the same side, and it was but the one lesion, it stood to chance that was the same lesion. That was the one

issue that did arise for that.

DR. FORESTIERE: The protocol required that all lesions be biopsied.

DR. FELDMAN: All stained lesions.

DR. FORESTIERE: All stained lesions would be biopsied.

DR. FELDMAN: Yes.

DR. FORESTIERE: Now, suppose there was some discrepancy in stained lesions and the visual examiner seeing a lesion that they thought should be biopsied, those all would be biopsied, as well, the visually identified lesion only?

DR. FELDMAN: One has the provision in the protocol for urgent biopsy at first visit, if that is the answer to your question. Without going for the second examination, we can biopsy at the first visit according to protocol. That is in-built, and that did happen in a number of these instances.

DR. FORESTIERE: What I am getting at is the discussion that may come up from the FDA reviewer that only I think somewhere around 45 percent of the lesions, the abnormal lesions were actually biopsied.

DR. FELDMAN: I can't comment to specific percentage. I know we had two lesions in Patient 424 with which he would not agree to biopsy, which were quite

obviously osteoradionecrosis, and there was a clinically salient issue that did stain, that demanded biopsy that confirmed recurrence of his squamous cell carcinoma. If you are talking about this small of a number, those two that were osteoradionecrosis, certainly half of that critique, it is not a clinically meaningful issue when the new lesion that is apparent is so dramatic and demands an immediate biopsy in this case. Also, the patient wouldn't agree to it.

DR. FORESTIERE: Let me ask something about this vital stain, the stain, because we heard information that it is more specific with carcinoma or that the stain is retained longer with the carcinoma cells.

My understanding is that this stain is picked up with trauma, irritation, inflammation, and that is the reason why there is this two-stage procedure to eliminate the potential for false positive and excessive biopsy.

Can you clarify that issue?

DR. BERNAL: Yes. What you said is correct. In fact, that deserves strong emphasis, because dead cells, cells that are damaged in any way will not have any selectivity in staining whether it is carcinoma, fibroblasts, lymphocytes that are damaged stain nonspecifically, but they do not stain mitochondria, and what will happen is that there is staining of the nuclei and

staining of nucleoli when looked at under higher power, but the staining retention time is very different in looking at living cells, carcinoma versus normal epithelial cells.

For example, after a wash of carcinoma cells, it depends upon actually the site of the carcinoma. For example, squamous cell carcinomas of the head and neck in general, squamous cell carcinomas of the lung will retain the dye for four, six hours after washing, whereas, normal epithelial cells will release it after about 15 minutes, and cells that are damaged will release it within maybe two or three minutes, so there is a rapid release.

However, after there is nonspecific staining, for example, in crevices, in areas of ulceration, there would be nonspecific staining neither in mitochondria, nor in the nuclei, but there is some binding to mucopolysaccharide, there is some binding to fibrous tissue, but in the clinical examination, this is where they know that it is not cellular staining, it is fibrous staining.

DR. FELDMAN: If I may come back with just a clinical comment about the nature of the lesions that were not biopsied, I think you are addressing the question of the 33 lesions identified visually on first examination and the eventual 15 lesions that were biopsied.

A large number of those were not apparent on the second visual exam. The question came about as to how to

biopsy a lesion that isn't there. We would expect this exactly, according to the Mashberg protocol, that over the course of 10 to 14 days, a lesion caused by trauma would disappear.

So, that would be consistent of series of additional studies on oral cancer detection and surveys of pathology laboratories, the penalty for biopsying defined as the total biopsies divided by the number of true positives decreases 55 percent when you use the toluidine blue in this study.

DR. FORESTIERE: Maybe this will come up further when we hear from the FDA report, and we can discuss it more specifically then.

Do you have any data on the patients enrolled subsequent to October '96?

DR. GREEN: No, as a matter of fact, we do not. As you can tell, the interim data analysis has been a sensitive subject, and all we have done is to report, and I will report today that we are at 673 patients. Our statistician tells us we are at 673 patients, and we have identified 25 cancers. Fifteen of them have been with OraTest, and zero have been found only with visual.

We are waiting for the FDA, or according to protocol we are going to do the analysis at 54 cancerous lesions, and that is going to be our next endpoint unless we

are mandated by the FDA or by this panel to do another interim examination.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I have a few questions. On your trial, at the first visit, there were 94 patients who had lesions that stained. Thirty-two of those patients didn't return for a second visit. Why was that?

DR. FELDMAN: By the way, we looked at this as a 33 percent failure to follow through for final protocol, probably double that in most RCTs, and we were concerned about specifically that, but we expect that the problems would be inherent in the patient population with whom we are dealing, and certainly in terms of the negative finding from the first visit as far as they might be concerned.

The other nature of this is that in many of the cases of these patients, their routine follow-up might be something greater than 20 days.

DR. SIMON: Second question. You identified 17 cancerous lesions. How many patients was that?

DR. FELDMAN: That's 17, isn't it?

DR. SIMON: So, it was 1 per patient.

DR. FELDMAN: It was 17, is it not -- 16 patients. It was one for one in my site, but apparently 16 overall.

DR. SIMON: Can you estimate from this trial how many biopsies would have been recommended or how many

patients you would have recommended biopsies on if you were not using the stain?

DR. FELDMAN: Can someone help me on this?

DR. GREEN: I don't think that we have that data. This is a lot of data available, epidemiology data, and, if you will, statistical data that come out of biopsies in general.

DR. FELDMAN: One is 7.

DR. GREEN: One in 7.

DR. SIMON: One in 7 what?

DR. FELDMAN: One in 7 is this figure. The figure used, there is either a new primary or recurrent disease in one of 7 patients.

DR. SIMON: That is not my question. My question is if you were not using staining, how many of these patients would have wound up having been recommended for biopsy.

DR. GREEN: We really don't know. That was not part of our protocol. Interesting question. Joel, if you want to address it, it has got to be the ones that you see the lesions on, although lesions are a clinical call, and in Joel's specific site, with a lot of patients that he sees, the decision not to biopsy is oftentimes just as critical as the decision to biopsy.

Joel, would you address that?

DR. EPSTEIN: He just answered my question for me. Basically, if you don't see the lesion, you can't sample it, so that is the first thing. I think we could surmise then by turning the data around, that the ones in which there was no clinical lesion identified could not have been biopsied.

Similarly, we have in high fraction radiated volumes, a real reluctance to push the biopsy on first assessment unless we are really suspicious of the clinical appearance of the lesion - lumpy, irregular, red and white, not just white, so we would have probably at least delayed meaning that we would need to see progression prior to biopsy.

DR. SIMON: The question was could you estimate the number.

DR. EPSTEIN: No, the study wasn't designed to do that, so I don't think we could.

DR. SIMON: The only other question I have then is do you have any auditing procedures in place for assuring quality control of this data?

DR. EPSTEIN: Study monitors you mean, yes.

DR. SIMON: Could you describe some of those procedures?

DR. GREEN: The clinical research organization that we have hired is not here today, but they make periodic visits to the sites. They initiate all the sites by doing

training of the people involved, and then over the course of the examination, they go back to make certain that if there is any change in personnel, that they are re-educated and that the study is being run properly.

DR. SIMON: Do they check the data that is submitted against source material at the sites?

DR. GREEN: Yes, they do.

DR. SIMON: I guess the thing that is sort of disconcerting is when we basically, we, as a committee, deal in assessing quality of information and what the information tells us, it looks like in this situation there is a lot of questions about the quality of the data, which is unfortunate, because there is obviously a lot of public support for having something that would effective for early diagnosis of these lesions, and yet we are dealing with trials in which there was basic concern about the quality of this data.

You come here and give a presentation in which you don't mention word one about anything about the data, just about why it should work and why it would be useful if it did work, and we are left trying to understand why there are all these questions about the quality of the data.

DR. FELDMAN: You have questions that you raise that are typical of any RCT. If you would like, the monitor left my place yesterday afternoon.

DR. SIMON: I don't think that is true. We typically don't deal with these kinds of concerns about the quality of the data.

DR. FELDMAN: As an examiner, I know I have to deal with these questions, let me put it that way. If you would like I can detail what our monitor did the last two days, Monday and Tuesday of this week.

DR. SIMON: You didn't present anything about your explanation of different interpretations between your view of the data and the FDA's view of the data. You asked us to somehow dismiss the FDA's position, but yet you don't present anything about why you believe your position is correct.

All you do is talk about why theoretically this may work.

DR. FELDMAN: We are talking about clinical data, sir. I don't think we are talking in theory here. We are talking about the presentation. I can describe how specifically it is that a monitor assures that the data collection has gone according to protocol.

DR. SIMON: That wouldn't address the issue of why we have all of the discrepancies that we have.

DR. GREEN: If I can, I agree with you, I think that certainly Zila Corporation, as an entity, and having not gone down this path before, in the first cohort of 367

has learned a great deal.

We have never been before this panel before, nor have we had a clinical study that has been done before, and I am sure that that is no excuse.

We have employed the best kinds of clinical research organizations that our money could buy. We have done 12 centers around the world. There is no question that we would prefer to be up here with more numbers, no discrepancies.

I think if I may address just the issue that you have raised in terms of our clinical presentation as opposed to, if you will, the discrepancies of the FDA reviewer.

I think that was, frankly, it was my decision, and I felt that in the presentation that we had to make today, that it was not going to be in the company's best interests -- we are talking about 17 lesions here -- and it seemed to me that this was kind of a he said/she said, and for us to go up there and say, you know, we have already given you data that says that, in fact, some physicians and some dentists missed lesions that somebody that read a clinical electronic data seems to think that they should be there.

I guess that other than giving you the data that has already been presented to you, there is not much else that we can present to you in terms of charts or graphs which will let you determine the validity of either

presentation.

Our only reason for doing the clinical side of it was so that we wouldn't get into this. We are waiting anxiously for the FDA reviewer to make his presentation, and in the final analysis, that is one of the reasons why we are here today. We only have 17. We have a subset of the screening tests that we have, and we think that it should be approved.

As I said in my statement, we are ready, willing and able to continue on with both the research on the clinical side and the chemistry side of it.

MS. BEAMAN: I would like to have known more about the toxicity of the OraTest and also what you would do in order to protect the patient after using the test. That is one comment.

The other is the statement references a statement that the staining or dyeing technique would indeed serve to frighten a tobacco user. I would recommend food coloring. It's a lot less toxic.

DR. GREEN: Thank you for those comments. As far as toxicity is concerned, as I mentioned in my beginning statement, this product has been used in medical communities since the early 1960s. It has been used as an I.V. solution for some medical diseases. Toxicity has never been a real issue. Safety, there has always been clean safety data.

Dr. Dolor wanted to add something.

DR. DOLOR: I just want to make one comment about I think there is some confusion about the purpose of this meeting. The purpose of this meeting I think was what was presumed to be a paper NDA, and that the data that was presented to you is an ongoing trial for an IND, and we were instructed that we could submit that preliminary data in support of a "paper" NDA.

So, you know, we weren't here, we didn't come with the purpose to show you the results of the screening trial and say that we need an indication for screening. We came here to discuss the original proposal, which was for identification of the lesions for biopsy, and so I just want you to keep that in mind.

DR. SIMON: But you didn't present any, you didn't present those reports either. You didn't present any data.

DR. DOLOR: Well, I think some data was -- there is some history with the correspondence between Zila and the FDA where there was some initial data that was presented that was felt to be acceptable, and then since has been rejected, so it is hard for us to go back and then just do a presentation based on those data that they thought would support their paper NDA.

Dr. Green, do you want to try to address that?

DR. GREEN: Obviously, there is not enough data,

but I certainly wouldn't say there is no data. I would say that if you take a look, we have sent out a booklet for everybody with our 22-volume NDA in it, and there is summary sections 2 and summary sessions 8.

The number of studies that have been done, I mean we can go over on a study by study basis, and, you know, FDA versus Zila in terms of the clinical data that has been there, but all we have to present to you is the 367 patients.

We did anticipate that this would be a paper NDA. The Johnson and Warnakulasuriya data study was reported by the FDA not to be with Zila's product. That is incorrect. It was with OraScreen, and it was done is Sri Lanka, and you have the data in front of you.

I wish the data were different, but this is the data that we have.

MR. GRUETT: I have a question on the toxicity of the drug. I had throat cancer, and would this be taken orally and then digested or is it taken and spit out?

DR. GREEN: One of the presentations I was going to do was to spend 20 seconds up here and gargle in front of you. That is all it is, is a gargle, and so it is spit out. We have done a number of studies. Obviously, we have taken studies, and we have done these, so the patients have swallowed the entire bottle, and the only thing that happens

when you swallow the whole bottle is your urine may turn blue, and your feces may turn blue.

MR. GRUETT: This leads to my second question about the toxicity. You are using chromium as one of the active ingredients, hexavalent form of chromium?

DR. GREEN: No. No, we have never used the hexavalent form of chromium, and that has been presented to the FDA on a number of occasions. Chromium 6, which is the chromium that you are discussing, we do have chromium 3 in our product, but not chromium 6, at the 0.001 percent level, which is the standard from the CMC Division.

The chromium that is in our product is at the level which is nutritionally safe and is approved. I think it is lower than what is available in drinking water as far as chromium is concerned, which is chromium 3.

DR. DUTCHER: Dr. Raghavan. No? All right.

In the interests of time, we are going to proceed with the FDA presentation. We will take like five minutes for people to get set up, and then we will go ahead.

[Recess.]

DR. DUTCHER: Just so everyone is aware, some of the members of the committee will be leaving. However, they have heard the sponsor's presentation, and they have carefully read the FDA presentation, so their votes will be counted based on the data that has been presented, knowing

basically that they have had an opportunity to hear any rebuttal of the FDA data from the sponsor.

Dr. Kobayashi.

FDA Presentation

Ken Kobayashi, M.D.

DR. KOBAYASHI: Thank you, Dr. Dutcher, the committee.

[Slide.]

I thank the committee for their work and effort spent so far in reviewing this NDA. The FDA presentation is complex and covers a great deal of material. In the interest of time, I will be moving quickly through many of the slides, and I thank the committee in advance for its forbearance in this matter.

There have been some modifications to the slides since they were distributed, and I again apologize for any confusion that this may cause. Please note that I will be summarizing my points as I go along in the presentation, so there will be no final slide with a summary and conclusions.

[Slide.]

I would like to acknowledge the agency review team for their hard work on this project. In particular, Linda McCollum and Ann Staten have been our contact people with the firm.

[Slide.]

OraTest, as you have heard is the trade name for a 1 percent preparation of toluidine blue, intended for use as a diagnostic adjunct in patients with oral lesions that are suspected to known to be malignant, to help in detection of all sites of cancer, definition of borders of cancerous lesions and selection of sites to be biopsied.

The committee is quite used to response rate and survival analyses, but we don't often bring diagnostic tests before you for your consideration. I would like to take a few minutes to briefly review some of the parameters that are relevant to this application.

[Slide.]

This slide depicts a standard 2 by 2 table relating the presence or absence of disease to test positivity or negativity. Sensitivity is defined as the proportion of patients with the disease who test positive. In this table, it would be number of true positives divided by the total number of patients with disease.

[Slide.]

Similarly, specificity is defined as the number of true negative test outcomes divided by the total number of patients without the disease. It is important to remember that sensitivity and specificity are defined in relation to the presence or absence of disease, and not to the test outcome.

[Slide.]

In contrast, positive predictive value and negative predictive values relate the test outcome to overall test outcome. The positive predictive value is the number of true positive test outcomes divided by the total number of positive tests. Note that the false positive rate would be included in the denominator.

[Slide.]

Negative predictive value is defined similarly, true negatives over total test negatives, and again, the false negative rate is included in the denominator.

[Slide.]

A couple of caveats regarding the use of the predictive value. These estimates necessarily depend on the prevalence of disease in the population being studied, because this affects the numbers of false negative and false positive tests.

Assuming that sensitivity and specificity will remain the same in two different populations, the population with the lower prevalence will have a higher number of false positives and a lower number of false negatives, thus, the positive predictive value will fall, and the negative predictive value will rise.

This is not a phenomenon that depends on disease characteristics, but rather solely on the prevalence of

disease. It usually requires a change in the inherent biologic characteristics of the disease within a population, not just its extent within that population, to affect a test's sensitivity and specificity.

Thus, sensitivity and specificity are preferable to predictive values in assessing a diagnostic test.

[Slide.]

Three studies were submitted for review. Study ZP 44389-01 about which we have heard much so far is the primary study upon which the FDA analysis relies. The other two studies are considered generally case series without prospectively written protocols. Both studies were conducted by single investigators.

The Epstein study directly applied toluidine blue to lesions that were already identified as suspicious on unaided visual examination. The Warnakulasuriya and Johnson study used a single rinse protocol, which as we have heard, has a slightly higher false positive rate than the double rinse method.

At this point I will depart from the slides at the request of the committee. There has been a request to review the regulatory history of this application.

The application, the IND No. 44389 to investigate the use of OraTest was initially submitted to the Division of Oncology Drug Products on 1-18-94. As we have heard,

there were previous discussions within various other centers and divisions within the agency dating back to, as Dr. Green has mentioned, 1991.

I can only speak to the record since its arrival in our division. This NDA, No. 20726, was initially submitted on August 7, 1996, containing the results of studies by Dr. Mashberg, Dr. Epstein, and Drs. Warnakulasuriya and Johnson.

This application was considered insufficient on its face to be acceptable for filing, so a Refuse to File letter was issued by the division.

Following that, the issuance of that letter on October 24, 1996, and again on December 11, 1996, conferences were held between the FDA, the Division of Oncology Drug Products, and the applicant, in which various issues were discussed related to the refusal to file.

In particular, the one that I want to focus on is that the applicant proposed submitting an interim analysis of Study ZP 44389-01 in support of this NDA. This proposal was strongly discouraged by the division on multiple occasions during those two meetings, however, the applicant indicated they desired to proceed with their proposal and they were advised to submit the data initially to the IND, so that the division could review it without having any adverse consequences to the NDA. The idea was that we would

be able to sort of vet the data and advise them on how best to present the data when it came in to the NDA.

On February 18th of 1997, the Division of Chemistry and Manufacturing Controls issued a letter, an efficiency letter to Zila, citing various deficiencies in the manufacturing processes.

On June 12, 1998, this NDA was resubmitted and with the previously mentioned studies plus the interim analysis of Study ZP 44389-01. Unfortunately, at this time, the data that was submitted in support of this study was again felt to be insufficient.

Primarily, one of the major issues was that the pathology reports were not submitted, and again, the application was refuse to file. I would point out that the applicant had been advised that the pathology reports and photographs would be important in the subsequent submission, in any submission, and this advice was rendered prior to submission of the June submission.

On September 3, 1998, the application was resubmitted, and was considered fileable, and that brings us up to this current advisory committee meeting.

[Slide.]

On to Study ZP 44389-01, the objectives were to determine the relative efficacy of toluidine blue rinse for the discovery of persistent, recurrent, or second oral or

oral/oropharyngeal malignancies in comparison to the conventional oral examination and also to determine the efficacy of the toluidine blue rinse for delineating the margins of the most significant biopsy site.

The application contains virtually no data to support the second objective and therefore we will focus our attention on the first objective.

[Slide.]

Please note that the patient population studied is very different from that identified in the label. The study population focused on patients who had completed primary therapy ov an oral or upper aerodigestive tract malignancy who were free of clinically evident disease and who were being followed in cancer screening clinics for the development of subsequent malignancies.

The population being targeted has lesions that are either known or suspected to be malignant, and the search is being conducted to identify other malignant lesions or to select a site for biopsy.

Thus, the prior probabilities in the two populations when assessing a lesion observed on the unaided visual examination are likely to be very different in the examiner's mind.

[Slide.]

Because the applicant's pivotal study was not

designed to directly support the indication in this NDA, the regulatory question faced was whether the study provided data that might support approval for the labeled indication or indications.

[Slide.]

Several questions were faced in the course of this review. Some of the more significant ones I have indicated here. We felt that this study could provide useful information relevant to this indication if it showed that OraTest revealed large numbers of malignancies in areas of mucosa that appeared completely normal.

Other important considerations in assessing any diagnostic test are the specificity of the test, since this is directly related to the number of false positive biopsies, whether complete information was available on all observed lesions, and how the sites to be biopsied were selected.

[Slide.]

Important considerations in evaluating any multicenter study, but particularly so for one which provides the sole or clearly most important support for an NDA are the consistency of study conduct and outcome across sites, the persuasiveness of the study's findings, and whether multiple endpoints involving different events were assessed, for instance, tumor diagnosis, resectability

rates, and so on, and so forth.

[Slide.]

Dr. Green has already presented this information, and in the interest of time, I will skip the slide.

[Slide.]

Inclusion criteria are shown here. Please note that the primary criterion was a previous diagnosis of either oral, oropharyngeal, or upper aerodigestive tract cancer including lung. This was not restricted to patients with squamous cell carcinoma, and although a summary of the histology will not be shown here, again in the interest of time, there were a substantial number of patients who were enrolled with, as best we can identify, lymphoma, salivary gland cancer, thyroid cancer, malignant fibrous histiocytoma, and other non-squamous cell malignancies for which the importance of the field cancerization paradigm is not clear.

[Slide.]

Important features of the study design from a review perspective were that each patient was evaluated by independent examiners, each of which was blinded to the other examiner's opinion, that all suspicious lesions were to be both photographed and biopsied, that all stained lesions were to be biopsied, that the histological examination was to be blinded to the clinical result, and

that a two-visit procedure was to be employed.

[Slide.]

Patients were routinely required to undergo two stain examinations before a biopsy, if indicated, was performed. However, as you have heard, there was an important feature of the protocol, which was a bypass mechanism allowing biopsy after visit one.

In the words of the protocol, these lesions were to be those which are felt to represent oral cancer requiring immediate action. In view of this provision, then, biopsies that were obtained after only one visit were assumed to represent such cases.

It also seems reasonable to presume that such biopsies indicate that there was some other feature besides the stain that prompted the urgency since it does not seem self-evident, at least to this reviewer, that a blue stain in and of itself would require such urgent attention.

[Slide.]

Turning to study conduct. The study, as we have heard, is still ongoing. The applicant selected a cutoff date of October 7, 1996, at which time 367 patients had been enrolled, 17 cancers had been diagnosed.

As we have heard today from Dr. Green, 673 patients have been enrolled, and 25 cancers have been diagnosed.

[Slide.]

Study enrollment was unbalanced by center, with one site enrolling more than twice the number of any other patients as in any other center. In this slide, the 5 centers which contributed patients to the efficacy outcome, meaning the 5 centers in which all the cancers were diagnosed, are highlighted in yellow.

All subsequent slides that I show that depict a by-site analyses use the same numbering scheme which is rank ordered according to number of patients enrolled. Please note that the patients were allowed to be entered on multiple locations, and, in fact, 19 patients were entered twice and 2 patients were entered three times. These patients are considered as separate patients.

[Slide.]

Eighty-five percent of patients completed this study, 15 percent were either discontinued, disqualified, or terminated from the study. Distinctions between these three categories are unclear, but they do include reasons, such as unspecified protocol violations, failure to return for visit 2, noncompliance, failure to use clinical trial material, enrollment within 6 months of a previous OraTest exam, and so on.

To answer Ms. Beaman's question, the only safety data submitted by the applicant was that 2 patients were

terminated because they were considered undue risks to continue, but no further elaboration was provided, and 5 patients discontinued of their own choice.

Recall in interpreting this figure that the protocol required a maximum of 3 encounters, which would be 2 examinations approximately 2 weeks apart, and possibly a third visit for a biopsy if it was not performed at one of the 2 examinations.

[Slide.]

The database that was submitted for the visual lesions, or at least identified on unaided visual examination, excuse me, contained a total of 226 separate entries. Since case report forms were submitted only for patients with positive biopsies, the electronic database forms the primary source of information on the majority of patients.

The official pathology reports differed from the electronic database in that they contained information on 10 lesions, which suggested that they were considered suspicious enough to warrant biopsy. In 4 instances, the database contained no entries for these lesions, and entries for the other 6 lesions were in the database, but were characterized as not suspicious.

It is critical to the review of this application to have a unique identifying number assigned to each lesion

if one is comparing whether lesions were identified by visual examination and stain examination.

The database contains such identifiers only for the lesions which were considered suspicious, those which are highlighted in yellow. Actually, there were 50 identifiers provided, not 49, but there was 1 lesion which was identified 3 times.

For various technical reasons, it was not feasible for FDA to proceed to assign unique identifiers to the remaining lesions, and therefore our analysis is mainly restricted to these lesions, at least for the unaided visual examination.

[Slide.]

There was some variation in detection rates of the visual examination across study sites. This slide depicts the study site, the total number of lesions that were reported as being identified on the unaided visual examination at that site, the number of patients in which these lesions were observed, the total number of patients enrolled per site, and the percentage of patients enrolled that these numbers represent.

You can see that the largest sites reported lesions in only 3 percent of patients. Other study sites reported finding lesions in 9 percent to 78 percent of the patients studied.

[Slide.]

FDA based its analysis on 44 biopsies in 37 patients and 18 cancers rather than 17 because duplicate biopsies of the same lesion were submitted for 3 lesions and 2 biopsies were reported by the surgical pathologist but not by the applicant. Both of these biopsies revealed carcinoma.

[Slide.]

There were 53 separate lesions identified on unaided visual examination and 80 lesions by the stain. Adjustments for lesions that were identified by both methods leaves 107 separate lesions that should have been biopsied, and only 44 of these lesions were, in fact, biopsied.

Again, a sensitivity analysis or specificity analysis that FDA conducted were based solely on this group of patients.

[Slide.]

There was also a difference in the number of biopsies that were performed across centers. This slide again depicts the site, the number of biopsies obtained at that site, patients enrolled, and the biopsy rate at that center, and you can see again the site having the largest number of patients had a rate of 1.53 biopsies per 100 patients, and there is a substantial difference between this rate and the rate at each of the 5 centers contributing

efficacy outcomes.

[Slide.]

In attempting to understand the differences that I have just noted, it was realized that the protocol did not clearly define what constituted a positive visual examination.

The applicant also identified the same problem, stating that, as you have heard, "The protocol did not anticipate that a biopsy recommendation as a result of the first visual exam would be reconsidered if the patient had to return for a second OraTest examination. If the lesion seen on the first visit had resolved and no longer looked suspicious, clinicians were allowed to overrule their initial order to biopsy and cancel the scheduled biopsy."

This was not included in the protocol, this provision was not included explicitly in the protocol, but appears to have been left to the discretion of the individual examiners.

[Slide.]

In attempting, then, to recreate a plausible decision rule for defining a positive visual examination, we considered that there are four reasonable choices.

In scenario 1, the test result would be based only on the results of the initial visit. Thus, a lesion which was suspicious on the first examination but not the second

would be considered positive.

Scenario 2 required that the lesion be identified on both visits. Thus, the hypothetical lesion would not be considered positive.

Scenario 3 allowed use of information from either visit. Thus, again, this hypothetical lesion would be considered positive under this rule.

The last scenario is a hybrid which was designed to take into account lesions identified as suspicious by the pathology report, but which were not included in the electronic database. It combines information contained in that database, in the final version, from scenario 3, together with clinical descriptions from the data sections of the official pathology report forms.

[Slide.]

In selecting which scenario to base this hybrid on, we looked at the prediction rates of the various decision rules. This slide indicates the site at which any biopsy was performed. Again, the total number of biopsies at that site.

This is the performance of each of the 4 scenarios in predicting the number of biopsies, so that taking, for instance, site 2, scenario 1 would have predicted that 3 biopsies should have been performed, for a 75 percent error, scenario 2 would have predicted 2 biopsies, for an 83

percent error, and scenario 3 predicted 4 biopsies, for a 67 percent error, and scenario 4 predicts 7 biopsies, for a 42 percent error.

This calculation makes the assumption, which was stated in the protocol, that any suspicious lesion would be automatically biopsied. The numbers highlighted in yellow here show the rule which minimizes the difference between the predicted number of biopsies and the actual number of biopsies.

The point here is that for sites 1, 4, 8, and 10, it is not clear which decision rule was used to call a visual lesion positive, and therefore to stimulate a biopsy.

The second point to be made here is that scenario 3 minimizes the error in prediction across all sites, and that is why this rule was selected as the basis for the hybrid decision rule.

[Slide.]

The criteria for defining a positive test would affect the test performance, and this slide quantifies that impact. The numbers of true positive, false negative, true negative, and false positive lesions are indicated here, categorized by the different scenarios.

The numbers cited by Zila in the application are shown up here for reference, and these two columns show the sensitivity and specificity that would be calculated under

each of these rules.

The point here is the variability. The number of true positive lesions detected by the different scenarios, depending on the rule that you used, can vary from 6 to 13, which is a 116 percent difference, and the sensitivity various then from 33 percent to 72 percent.

The cost of the examination in terms of missing cancers is shown by the false negative rate, which varies from 5 to 12, which is a 140 percent difference, and the cost in terms of potentially unnecessary biopsies, which is reflected by the false positive rate, varies from 5 to 18, a 260 percent difference. This is reflected in the specificity estimates, which ranged from 31 percent to 81 percent, again a more than 2-fold difference.

Therefore, the consistency in which a lesion was considered positive matters.

The analysis according to scenario 4 is shown on the bottom line here and indicates that this rule has a 72 percent sensitivity and a 31 percent specificity. For comparison, studies reported in the literature cite estimates for the unaided visual examination of a 74 percent sensitivity and 99 percent specificity.

[Slide.]

The protocol defined a positive stain as one which stained the lesion on both the first and second visits. An

exception was made for cases which were biopsied urgently, in which only the result from the first visit was used. FDA interpreted this as being lesions which stained on both visits, unless only one visit was recorded, in which case the stain result from that exam was used.

[Slide.]

The database contained 204 separate entries for stained lesions. Because patients were examined on two separate occasions, inevitably, some of these entries refer to the same lesion. That is what this table tries to convey.

These patients here in this column were examined on two separate occasions, these patients here were examined on only one occasion. So, these are the patients who stained on the first of two visits, the patients who stained on only one visit, patients who stained only on the second visit, the patients who stained on both visits, and these are the duplicate stains of these patients. Again, this discrepancy is due to the fact that one lesion was stained three times on two separate occasions.

Two-thirds of patients who had positive stains were called positive because they were visit 1 lesions, and one-third stained on both visits.

[Slide.]

Only 49 percent of positive-staining distinct

lesions were biopsied. Since the protocol required that all lesions that stained positive should be biopsied automatically, it is unclear why the case report forms and database would contain a recommendation for biopsy based on the staining characteristics. Nevertheless, 25 percent of the entries in the database contained such a recommendation for stained lesions.

[Slide.]

This slide again depicts the impact of the test definition on outcome. Overall, the stain identified 16 malignancies in the FDA analysis, which were evenly split between lesions that were identified on both visits and lesions which were identified on the only visit.

[Slide.]

This table restates in some sense the previous table, and compares the FDA analysis with Zila's analyses. These are the two lesions that were missed by the stain. As you can see, the estimates of sensitivity are different, but within the limits of the data are probably quite similar. The estimates for specificity are quite close, and show that the test has a specificity of approximately 17 to 19 percent, which is low, and which translates into 20 to 21 potentially false positive biopsies.

[Slide.]

This is an unplanned interim analysis. The

applicant's plan for interim analysis is shown here. It was based on the number of positive biopsies rather than on the number of enrolled patients, and thus, the first interim analysis should have been conducted at a point when 54 positive biopsies had been identified.

Under this plan, the nominal p value required to declare a significant result at the 5 percent level in the primary analysis would be 0.00505.

[Slide.]

The applicant conducted this analysis after 17 cancers had been diagnosed, and found a p value, as you have heard, of 0.004. This slide compares the performance of the unaided visual examination with OraTest among lesions diagnosed with cancer, and correlates positive and negative tests with each other.

The comparisons of interest in this slide are the off-diagonal quantities, highlighted in yellow, which show instances in which the two tests gave different information. With apologies to Dr. Simon, a significant result in the McNemar test would indicate that the two tests yield different information, but it does not necessarily indicate the direction of that difference.

[Slide.]

This is the FDA's analysis, which shows the two positive lesions, two malignant lesions missed by OraTest

and five lesions that were identified by OraTest but missed on the unaided visual examination.

If you will recall, the applicant Zila claimed numbers for these cells would be zero and 10. This table returns a nominal p value of 0.227 in the McNemar test.

[Slide.]

Assessing the compliance of the protocol investigators with the protocol requirements. To address, I think Dr. Forestiere's question, the requirement for independent examiners that the unaided visual examination examiner be independent of the OraTest examiner was followed pretty well. In only 2 percent of this patients was this violated. I would point out, though, that this primarily occurred at one site which enrolled 41 patients, site number 4.

No photographs were submitted.

The pathology reports on 20 out of the 37 patients contain some indication of the staining characteristics, either an explicit statement or an inclusion of the study code which identifies the stain characteristic of the lesion.

Thirty-one out of 53, or 58 percent, of lesions on the unaided visual examination and 46 percent of lesions which stained positive were biopsied. Overall, depending on the decision rule used for the unaided visual examination,

between 41 percent and 48 percent of distinct lesions were biopsied, and 35 percent of patients with positive stains were examined only once.

[Slide.]

Turning to a case-by-case analysis of the diagnosed lesions, this table depicts the lesions according to how they were identified. This table differs from the applicant's analysis in a few ways.

First of all, the highlighted lesions would be ones that were claimed by the applicant to have been identified only by the stain with the exception of this lesion, which was not recorded by the applicant, but which was shown on a surgical pathology form.

Lesions identified with two asterisks were enrolled at site number 4, and all four were disqualified by the investigator at that site.

[Slide.]

Postponing discussion of patient 106 to a subsequent slide, the lesion of interest in patient 199 was identified as a carcinoma by the unaided visual examination on visit 2, a biopsy was recommended, and the pathology states that slow-growing lesion had been present for 2 months.

For patient 321, there was no visible lesion recorded on the case report form, however, the pathology

report states that the patient had had a 5-month history of a sore on the right side of his mouth. The patient was biopsied urgently on visit 1, and he was observed to have lymphadenopathy in the right neck.

[Slide.]

Patient 376 again had no lesion documented for the unaided examination on the case report forms, however, the pathology report states that this was an incisional biopsy of an ulcer which stained with toluidine blue, and the biopsy was again performed on visit 1.

Patient 379, the lesion of interest was identified by the unaided visual examination, but it was diagnosed as a leukoplakia. However, the patient had new onset of lymphadenopathy in the interval between visits 1 and 2. The pathology report form states that there was a 1 by 1 mm lesion on the right buccal mucosa. Biopsy was not recommended, however, there may be some controversy about this issue, because it is frequent clinical teaching that leukoplakia, particularly in a high-risk population such as this, should be biopsied.

[Slide.]

This depicts the case report forms for patient 106. This is the form for the unaided visual examination. This is the form for the stained lesion.

The patient had a history of an expanding mass and

trismus. Two lesions, one on the left tongue, which was identified as 023, and one in this region, which appears to be the retromolar trigone, it is difficult to tell, which was identified as 013, were identified as carcinoma. They required urgent biopsy on the unaided visual examination.

Neither lesion, as you can see, stained with OraTest however, the stain did detect one lesion, labeled as T13, on the left alveolar mandibular ridge. The local pathology for these lesions, for these biopsies, was submitted for central review on 5-8-96, and the records indicate that the central review agreed in all major respects with the local pathology.

[Slide.]

This shows the pathology report for this patient and excerpts from the case report forms. I am sorry that I don't have a specific identifier on this. You will have to take my word for it, I guess.

The applicant claims that the stained lesion T13 showed carcinoma, and that this lesion is an instance in which only the stain indicated malignancy at that site. There is also the notation that the visually detected lesions were not biopsied because the patient was referred for a CT scan.

The pathology report indicates that on 8-2-95, three lesions were biopsied, one located in the retromolar

trigone, one located on the left lateral tongue, one located on the left mandibular alveolar ridge. The biopsies on the retromolar trigone and the left lateral tongue showed carcinoma. It appears that one of these was 013, one of these was 023.

This appears to be the stained lesion. It is labeled biopsy of the left mandibular alveolar ridge, and you can see that the pathology report states that is a fragment of hyperplastic squamous epithelium with submucosal fibrosis.

[Slide.]

This patient is stated to be an instance in which OraTest identified two carcinomas in situ. Again, this is a reproduction of the case report form for the stain exam. The two black spots here indicate the lesions as identified by the applicant for the two lesions, and it does appear that there are two separate lesions. However, please note that each gridlock represents 10 by 10 mm.

The larger lesion is stated to measure 25 by 30 mm, and the grid location specified on the case report form indicate that this larger lesion should indicate these boxes here. These red spots in the middle of the blackened areas are sort of an approximate representation of the locations from which the biopsies were taken.

Lesion T13, the smaller one, was identified on

local review as having no pathologic diagnosis. The larger one was identified as carcinoma in situ. Central review revised this lesion's diagnosis to carcinoma in situ. It appears that this may have been an instance in which two biopsied were obtained from the same lesion.

I apologize. The numbers that I cited to you showing positive biopsies, and so on, and so forth, don't make note of this because this issue was identified only within the last two days, and we didn't readjust the analyses.

[Slide.]

Patient 404 had no lesions recorded on the unaided visual examination. However, there are several circumstances about this claim that seem relevant in evaluating this claim.

The lesion is recorded as having an equivocal stain, and yet it was biopsied on visit 1. Recall that biopsies on visit 1 were to have been performed only when there is a special urgency about the lesion that made it imperative to make a diagnosis immediately.

In this regard, the patient was one in which there was no lymphadenopathy recorded on the physical examination. The patient was enrolled at site 4, and was disqualified by the investigator for failure to return for visit 2.

The clinical report for the pathologist stated

that it was a lesion which stained positive with toluidine blue. The local pathology showed epithelial dysplasia, severe epithelial dysplasia, evidence of microinvasion, and this was revised on central review to carcinoma in situ.

[Slide.]

Patient 424 was noted to have clinically evident lymphadenopathy on the first visit. He had two lesions identified on unaided visual examination. One was identified I believe as benign leukoplakia, but in any case, no biopsy was recommended.

A tongue lesion was identified on the unaided examination, diagnosed as an ulcer. A biopsy was recommended, but no biopsy was performed.

Three lesions were identified by the stain. This lesion here was not identified by the stain. The ulcer, the lesion identified as an ulcer, was identified by the stain. A second lesion on the other side of the tongue was identified by stain, as well as a lesion on the floor of the mouth. The floor of mouth lesion was biopsied and shown to contain carcinoma.

[Slide.]

In summarizing Study ZP 44389-01, there are a number of concerning issues, which are enumerated on this slide. The population studied is different from that in the labeled indication.

The study was stopped when only 10 percent of the intended patients were accrued.

A large number of patients were enrolled whose data were not submitted.

Positive outcomes in too few patients were observed.

FDA has reservations about some of the other positive outcomes observed.

[Slide.]

Multiple important protocol violations were noted.

There were multiple discrepancies between the case report forms, the pathology reports, and the electronic database.

Study outcomes were inconsistent across centers.

FDA is unclear how certain sites were selected for biopsy.

Many required biopsies were not performed.

[Slide.]

The test criteria for the unaided visual examination were not clearly defined and may have been applied differently across centers.

There is a 15 percent rate of patients who were disqualified, discontinued, or terminated.

The specificity of this test is low.

There are important consequences to a false-

positive biopsy.

[Slide.]

This study was identified by the applicant as pivotal to the NDA, and for that reason is being presented.

[Slide.]

It was conducted by a single, highly experienced investigator at the British Columbia Cancer Agency over a six-year period. Patients were referred for evaluation by community dentists. The method used in this study differed markedly from the proposed method. It is unclear to what extent the investigator's training and experience can be extended to the general community practice.

For these, among other reasons, it is felt that this study provides little support for this application. Since it was discussed earlier, I will present a few points about this.

[Slide.]

Important points are that there was no written protocol, so that the criteria for determining test outcomes are not known and may have evolved over time.

It appears to have been the author's practice to routinely review the pathology personally, and both his interpretation and the official pathology reports were submitted.

Primary weight was given in the FDA analysis to

the official pathology report.

I think that was the only point I wanted to make about this slide.

[Slide.]

These are selected lesions about which the pathologist's interpretation and the investigator's interpretation differed.

[Slide.]

Based on considerations such as those just outlined, eight instances of malignancy were downgraded to nonmalignant diagnoses or to a missing report category which contributed no information to the analysis.

[Slide.]

Despite these issues, the applicant's and FDA analyses for sensitivity and specificity were quite similar. They show a 100 percent sensitivity for OraTest, between a 45 and 52 percent specificity for the stain.

However, this is not surprising since any lesion to which the stain was applied is by definition suspicious, and no data were supplied regarding lesions that were not stained.

I will go ahead and skip the next slide in the interests of time.

[Slide.]

As in the last instance, the applicant has

identified this study as important to the NDA and it is being presented for that reason.

There is an administrative nuance to this that is of importance. The data were submitted to an entity within the FDA called the Drug Master File, whose contents are confidential to everyone except FDA and the owner of the DMF. In this case, the owner is King's College, London, and FDA was given permission to reveal these data publicly by Dr. Newell Johnson, who represents King's College in this matter.

The applicant's analysis was based on the published paper since they were not granted access to the file's contents. Thus, we will be showing only the FDA analyses.

[Slide.]

The study was conducted at multiple sites in Sri Lanka and Pakistan by a single examiner. There was no written protocol, although a research proposal was apparently written but not submitted for review.

Method used was a single rinse.

The paper stated that the histology was reviewed by two independent pathologists at the Royal College of Surgeons, but the applicant has confirmed that it was the author's practice to review the pathology slides personally.

[Slide.]

It appears that the author his own interpretations along with a coded diagnosis from the official pathology report form, and it appears that the published paper relied on the author's interpretation of the histology slides.

The data was submitted as xerox copies of handwritten spreadsheets, and a comprehensive key was not provided for the abbreviations and codes used.

[Slide.]

The point of this slide is to indicate the extent of missing data. The RCS number is the Royal College of Surgeons accession number. We made the assumption during the review that if there was an entry for this number for a particular lesion, it meant that the lesion had been reviewed by a pathologist. If there was not a number, an entry for this number, we assumed it was not reviewed by a pathologist.

The punch line here is that 63 percent of slides were reviewed by a pathologist, and the report was entered into the database, 23 percent of lesions. The total number of lesions were reviewed, but the report was not entered.

[Slide.]

For a number of reasons, only 108 lesions were considered evaluable. The criteria for evaluability were that an official report code, pathology report codes were present, and there was an assessment of the stain outcome

and an assessment of the visual examination outcome.

Since the records were entirely handwritten, legibility was an issue in a few instances, but not many.

[Slide.]

It appears that 6 lesions were upgraded by the author of the paper to a diagnosis of malignancy, but these were apparently read either as having missing biopsies or as apparently benign diagnoses by the pathologist, 16 instances of malignancy were credited by FDA, although please note that one instance of the malignancy, one of the verrucous carcinomas was considered inevaluable because there is no stain result noted.

[Slide.]

Our analysis is shown here. OraTest is shown to have a 100 percent sensitivity and a 30 percent specificity. It did identify one malignancy which was not identified by the visual examination.

[Slide.]

Translating this data into a McNemar test type 2 by 2 table, the p value is 0.5.

[Slide.]

The final slides summarize our concerns with this study. There was a large amount of missing data. The staining method is different from that proposed in the label. I will remind you again this is a single rinse

protocol as opposed to the double rinse protocol.

Lesions identified in the submitted photographs are generally large, fungating or exophytic masses that are frequently obvious. It is unclear to what extent this experience can be translated to the general community practice in the United States.

[Slide.]

This is an example of one such lesion. This is the unaided visual examination. This is the stained lesion.

[Slide.]

In other words, the severity of disease at presentation appears to be greater in this population than in the United States, and therefore the sensitivity and specificity of OraTest may differ significantly in the two populations.

The prevalence of disease may also be greater in this population than in the United States, making assessments based on predictive values difficult.

This concludes the FDA presentation, and I thank the committee for its patience.

DR. DUTCHER: Thank you for a very succinct and very complete analysis, and for doing it so quickly.

Do we have questions for FDA? Dr. Simon.

Questions from the Committee

DR. SIMON: You went by it fairly quickly.

DR. KOBAYASHI: I was asked to do that.

DR. SIMON: What were the conditions under which a lesion was biopsied, either in the protocol or in actuality?

DR. KOBAYASHI: Yes, sir. I cannot comment as to what the conditions were under actual use. The protocol specified that a lesion which was identified as positive on the unaided visual examination was to be biopsied and that any lesion which stained positive with OraTest was to be biopsied.

DR. ALBAIN: Could you clarify further what you mean by identified as positive, meaning the clinician suspected that it was a malignancy or the clinician was concerned enough such that in usual practice that would be biopsied?

DR. KOBAYASHI: No, I cannot comment on that. I am not entirely clear what the protocol meant by a positive visual examination.

DR. GREEN: Your observation is correct.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: Was there any indication from the data monitoring group that one institution which put on so many patients had such a low biopsy rate, that that fell out of what was to be expected in terms of how the protocol was interpreted, and was there any notice given to that institution that there was a problem?

DR. KOBAYASHI: Right. No, ma'am. The NDAs usually do not contain the reports of the sponsor's monitoring reports. FDA does have a component, the Division of Scientific Investigations, which goes out and sort of audits the study sites, however, their audit is currently in progress, we don't have their report yet.

DR. GREEN: As part of that monitoring effort, I have a letter from Dr. Jones Johnson, Office of the Director, University of Pittsburgh, Department of Otolaryngology, that I will be submitting to the FDA.

The substance of this letter basically says that in the Department of Otolaryngology at the University of Pittsburgh, they are surgeons first, and they have, in fact, screened out all of the suspicious lesions, and any person who came through the clinic that had a suspicious lesion was surgerized, and he has memorialized that in writing.

We have discovered it, it has been monitored, and for the rest of the cohort beyond his 131, he is now back in line.

DR. FORESTIERE: So, you are saying that none of those patients went on to a second visit, in other words, so at the first visit, if there was a suspicious lesion, they went off for surgical treatment?

DR. GREEN: Yes, ma'am. They were not enrolled.

DR. DUTCHER: If they had an obvious lesion, they

weren't enrolled in the study, is that correct? They were just taken to surgery.

Dr. Simon.

DR. SIMON: A couple of questions. One, it seems to me that it is really key in interpreting the data from that study what the conditions were that led a lesion to be biopsied. For example, if you preferentially biopsy lesions that are found to stain on one or both exams, then, the sensitivity of the stain is artificially going to look better than visual exam, because you can't really calculate validly sensitivity when you decide what to biopsy based on your test.

If you decide what to biopsy based primarily on a staining test rather than in a visual examination, then, your sensitivity is going to look higher for the stain than for the other just because you will biopsy a certain number, a certain number will be positive, and you will say, yes, they stain positive. Well, they stain positive because that is the reason you biopsied them. I mean you biopsied them because they stained positive.

I guess I just don't see how --

DR. DUTCHER: That is the point.

DR. GREEN: Yes.

DR. DUTCHER: That is the point. If you have things you biopsy that are positive that you don't see,

then, that makes this a valuable test. If everything you biopsy is what you already saw --

DR. SIMON: But I guess the point is though, also, what you get is we got so many more lesions here identified this way than the other way, but it is not a valid measure of sensitivity, and the McNemar test is also not really valid. What you really get is how many lesions you found that were positive from the biopsies you did with one approach than the other.

I guess the other question I wanted to ask, you raised earlier in your talk the issue of what data is contained, what information do we have in this trial that is actually relevant to the indication being asked about.

Can you sort of summarize that?

DR. GREEN: Would you mind if I talked to your first question?

DR. DUTCHER: Dr. Kobayashi is supposed to answer that one.

DR. GREEN: I asked if I could.

DR. KOBAYASHI: Yes, sir. That is an issue that we have struggled with within our agency, and it goes somewhat to the issue about the p values, as well. We recognize that there are problems with applying the McNemar test to this small data set.

Nevertheless, we felt that it was important to

present that data since there are assertions about p values, and so on, in the application.

How one takes this data is a little bit more difficult to decide. One can take the view that it is an unplanned interim analysis, that you should judge the study according to what it was designed to do, did it do the job it did, does it show what it was supposed to show.

That is kind of difficult to do because of the small numbers involved, the issues about the unplanned interim analysis, and so on.

The other approach that could be taken is to see, well, was the number of lesions that they found that weren't identified on the unaided visual exam good enough considering the specificity of the test to show something, was it good enough for approval in essence.

I think that after extensive discussion with Dr. Temple and internally, we have decided that we will try to make the best case that we can for the indication.

DR. JUSTICE: I think, to follow up on that, I think what our answer to your question is, we think they found five lesions by stain that weren't there visually. The company thinks they have 10, and there is 5 that there is some disagreement about.

DR. SIMON: I thought the indication was -- what I was really trying to address was the discrepancy between the

setting of this clinical trial and the indication, and I thought the idea was, the indication being requested, in terms of was looking in an oral cavity where maybe you already know that there are some lesions, looking for identifying other lesions in that sort of setting.

DR. D. JOHNSON: The indication on your third slide, Dr. Kobayashi, was the proposed indication was as a diagnostic adjunct in patients with oral lesions suspected or known to be malignant, to help in detection of all sites of cancer, definition of borders of cancerous lesions, and selection of sites to be biopsied.

I think Rich's point is, is that the study that they presented to us is actually a different group of patients with a different intent, and so the data we have been presented very tangentially deal with this issue, very tangentially, and we weren't really presented any data to substantiate the claim. That is really the issue.

DR. KOBAYASHI: I understand and I agree. We presented the data that we had available for analysis. I am hedging because I am looking for a sheet within the stack of papers.

DR. D. JOHNSON: While you look, I guess maybe it's not time to discuss, I was going to have some prediscussion. Do you want me to wait?

DR. KOBAYASHI: No, that's fine.

I am doing this from memory on an analysis that I just did actually at 10 o'clock this morning, so I can't speak exactly to the numbers.

There were approximately 11 or so, a small number of patients with lymphadenopathy. If you take the position that in a patient who has no visible lesions, you have one index of suspicion for cancer, but that in a patient where you have a known site of malignancy, you are going to have a higher index of suspicion for cancer.

You might also reason that if you have a patient who has evident lymphadenopathy, your index of suspicion for looking for cancer would also be higher. So, that group of patients might represent something closer to the indication.

It turns out, as I say, there was a small number of those patients, and amongst those patients I think the sensitivity for OraTest was 60 percent, and the sensitivity for the unaided visual examination was 75 percent. I can't recall what the specificities are. They actually may be at my chair there.

Again, I would caution you that I did this analysis this morning. I haven't had a chance to fully go through and basically tear it apart, but that may be somewhat helpful.

DR. JUSTICE: If you want, I have a piece of paper here. You said for stain, the sensitivity was 50 percent,

specificity was zero. For visual exam, sensitivity was 75 percent, specificity, 60 percent.

DR. DUTCHER: These are people with known lymphadenopathy?

DR. JUSTICE: Lymphadenopathy.

DR. KOBAYASHI: Clearly, one doesn't want to rely on my memory.

MR. GRUETT: Are there any other drugs on the market that conclusions can be drawn from that are similar?

DR. KOBAYASHI: No, sir.

DR. DUTCHER: Dr. Justice.

DR. JUSTICE: Just to follow up, I think the positive spin that we were trying to make for the company here was that even though the population was different, OraTest could detect five additional lesions that weren't detected by visual exam. A naive way of looking at it would be, well, isn't that good, doesn't that find some cancer that we are not otherwise aware of.

The other concern, though, gets into the specificity issues and the cost of a lot of extra biopsies, and that's the down side obviously.

DR. DUTCHER: Just to comment, I mean it seems that a lot of things that were identified as lesions did not get biopsied.

DR. KOBAYASHI: Yes, ma'am.

DR. DUTCHER: Do we have any idea what happened in that situation? I mean do we have any follow-up?

DR. KOBAYASHI: That is a complicated question, and it relates in part to the fact that unique identifying codes were not assigned, numbers were not assigned to all the lesions. I was able to see that a few lesions were seen as suspicious on the first exam, persisted on the second, but were downgraded to something that was not suspicious, not considered suspicious.

However, those are places where the lesion is clear, in essence, the grid numbers are identical. However, in looking at the way that the sponsor assigned the unique identifiers for the suspicious lesions, it was a complicated rule, and I didn't want to try to reproduce that and get it wrong. So, I really can't answer that question adequately.

DR. DUTCHER: Any other questions for FDA?

[No response.]

DR. DUTCHER: Thank you.

Committee Discussion and Vote

DR. D. JOHNSON: I have some comments to make, and I opened my questions with the first comment, and that is, the study that was presented was not designed to address the question for which the sponsor is seeking an indication.

Even if we were addressing that, the data that have been presented, such as they are, are wholly inadequate

to support any indication in my view, and I think it is disappointing, frankly, that the company came forward with this information in this format.

I cannot think of a single credible scientific organization that would accept such data. If we were an ASCO abstract review program committee, we wouldn't accept these data as preliminary report data.

Certainly, from my perspective, I applaud them for planning the study, and I think they ought to carry through with their planned study, and then analyze their data and then come forward with the data once they have completed their study.

They may have a very good product here that would do all the things that they have indicated today that they hope it will do and that the public speakers have spoken to.

With regard to the indication that they have sought, as I said, I don't think they have presented any data, and despite FDA's efforts to try to help them analyze their data in a very convoluted way, albeit fair and kind and benevolent, I don't see how we can approve the product for that indication.

To answer Bob, finding five cases of unsuspected cancer in 367 or so patients, at the risk of not knowing anything about the number of false positive studies, in my view, again does not warrant approval.

I think most of these patients are patients that are high risk, and would be followed closely anyway, and I happen to differ with some of the experts who the company has presented forward here, with the urgency with which one needs to identify CIS in a patient with a past history of head and neck cancer. I think it is a relative term of what urgency is.

Since my practice is heavily into that area, I feel reasonably comfortable in making that statement. So, I, unfortunately, don't really see that we have heard anything today that really sounds like a valid presentation from the standpoint of making a regulatory decision.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: I have to echo Dr. Johnson's concerns, but I have another concern, which is to tell the company to go back and complete the study. I am not sure at the end of another 300, 400, 500 patients we are going to have any other data that is any better, that is going to be any less confusing if the study is carried on the way it has been in terms of the quality of the data or the interpretability of the results.

MR. GRUETT: As a patient or a cancer survivor, I can see a definite need for a drug like this. In my case, it could have made a tremendous difference. I also have to agree with Dr. Johnson's findings.

You have got to get your stuff together, folks. Listen to the FDA. I think the cooperation from what I read is there, in their behalf. Start over and do a good job. If you feel you have got something good, let's present it as you feel the product is.

DR. DUTCHER: Other discussion, comments?

[No response.]

DR. DUTCHER: We have a series of questions that FDA has put together. I think we have discussed around them. Maybe some of the discussion can be helpful in trying to tease out some approaches that may give us a little more solid information in the future. Perhaps it would be a helpful exercise to go through them.

There are some tables on the second page which show the results as currently exist. There are some questions.

Question No. 1 discusses does the committee believe it is appropriate to combine carcinoma and carcinoma in situ categories for analysis? Any comments?

DR. D. JOHNSON: I would personally say yes. I mean I think we heard fairly definitively that these lesions CIS do progress, and I think it is important to know if a patient has carcinoma in situ. We are interested in this in all diseases and where something can be done, so I think it is important to determine that.

In my view, the company made a lot -- not a lot -- but made some points about how that seemed to be an issue. It might have been at one point for FDA, but I think for those of us who see these patients, CIS, in my mind, finding that is as important as finding early minimally invasive disease. So, I think we should count the two as one and the same from my perspective.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: I agree, but I think it underscores the need for independent pathologic review because severe dysplasia is a continuum in terms of how you read that, and if you are going to have a cutoff of severe dysplasia, no, but carcinoma in situ, yes, you have to make sure that you have an independent pathologic review that is not biased.

DR. DUTCHER: Dr. Forestiere.

DR. FORESTIERE: I certainly would agree that carcinoma in situ is a precursor lesion. You know, we know that that is going to go on, and I think that what the company presented was very accurate in their succinct statement about why it is important to include carcinoma in situ. I think it is perfectly appropriate.

I also agree with the issue of very careful pathologic review.

DR. DUTCHER: All those who would vote yes?

[Show of hands.]

DR. DUTCHER: Nine.

Not voting?

MR. GRUETT: Not voting. I don't totally understand the issue.

DR. DUTCHER: Okay. Yes. And then we have yes from the other three. Twelve yes, one abstain.

The second question. The FDA review confirmed only 5 of the 10 carcinoma/CIS lesions in the Zila study that were said not to have been visually identified. This conclusion has a substantial effect on the question of whether OraTest can detect non-visible malignant lesions. What is the committee's view on this analysis?

I think this becomes a matter of numbers, small numbers. Are we going to argue over 5 and 10? What Dr. Johnson said I think is the case, that if you don't know what the false positive rate is, how do you -- any other comments on that particular issue?

DR. SIMON: I think the other comment I have is that I mean this is fairly crucial, and it brings into question quality control. I mean it sort of raises basic questions about the data and the way it has been reviewed and independently assessed. I think that the company needs to deal with that in terms of future analysis.

DR. DUTCHER: Is that something they can do

prospectively?

DR. FORESTIERE: I was just going to say that I think there is a larger issue here. It is not really just 5 versus 10. I think there is a lot of discrepant information, and the whole discussion today has really centered around the quality of the data, indications for biopsy, when that was done, when it wasn't done, what happened to those patients. We have got a lot of holes here.

So, I think that the actual numbers of 5 and 10, given that we are dealing with a very small number of patients, is just indicative of the broader issue here and why we are coming with the stance that we are today.

DR. DUTCHER: So, what we are saying, I think, is that we don't really care what the numbers are right now. What we care about is being able to understand globally what happened to all the patients and what the true false positive and false negative rate actually will be.

No. 3. Does the Zila screening study in people at increased risk for cancer, a different population from the proposed indication, support the effectiveness of OraTest in detecting non-visible lesions at a useful rate? Does it also demonstrate acceptable specificity?

I think we just answered that. We just said we don't have that information.

We have to vote no, not sufficient information on that particular question.

No. 4. If the committee does consider the data from the Zila study as supporting OraTest's usefulness, should additional information be provided prior to approval?

I think the answer is yes.

From what, from the screening study, from another study in another setting, what recommendations do we have?

DR. D. JOHNSON: Well, I have already said I personally think they should complete their screening study, and I concur with the comments made regarding the quality of the data, you know, garbage in, garbage out phenomenon is alive and well, so that has to be dealt with.

However, they also came forward with another proposed indication today that is different in one respect than the screening test, and I think they need to conduct a second study in that group of patients if they are going to seek that proposed indication, namely, defining the borders of the lesions, known, identifiable lesions.

That is a different issue. It is an important issue it seems to me. But that would require, I think, a different study and one that could be conducted, because the standard of care now would be not to do that, and I think one could do analyses of patients who had their lesion removed with or without staining.

So, I think they need another study for that purpose if they wish to go forward with that.

DR. DUTCHER: All those who would agree that they should complete the screening study?

[Show of hands.]

DR. DUTCHER: Eight. Eight plus 3 is 11 yes.

And no?

[No response.]

DR. DUTCHER: Abstain?

[Show of hands.]

DR. DUTCHER: Two.

Comment?

DR. FORESTIERE: Again, I think that I am not sure that -- there are already 600 and something patients on this study, and there is a lot of problems with it, so I am not sure that adding in another 100 or 200 patients, whatever that total number, would make it any more interpretable than it is. In fact, I doubt it.

So, it seems to me that one has to kind of rethink this whole question and look at this is the indication we want, and do a study that specifically is addressed for that indication. I don't think that completing the current study will help with this particular request.

DR. D. JOHNSON: I guess one comment that I would make, I am afraid you are probably right, Arlene, but it is

my understanding from the review of the material that all the lesions were to have been photographed. It is my understanding the FDA did not have access to those photographs or that material. Is that correct?

DR. KOBAYASHI: You are correct in that all lesions were to be photographed. No photographs were submitted. In response to a question, an inquiry to the applicant, we were told that photographs have been taken, were stored with the patient's individual files.

It is not clear if those were the clinical files or study files, and that they could be made available upon request.

DR. D. JOHNSON: Again, I am not here to design the study for the applicant or salvage what they have, but it seems to me that from what Dr. Feldman did in his presentation, if he can train a dental hygienist to identify lesions, he could probably train someone like me to identify those lesions, and an independent group could review those, and it might be helpful, I don't know.

I mean it would be important to see. I don't know what the quality of those photos might be. The company might seek a way of getting independent confirmation of those data. I mean I could see ways of -- some of what we saw today, I sense was absence of information that might be available.

It is not just a question of didn't get done or wasn't done properly, it was just absence of data, and if those data are available, and can be reviewed and put in a proper format, then, it might be appropriate to go forward, but if what we see is what we get, and the other 300 patients that have been entered in have that same quality of data, then, I would agree going forward with another, however many it takes to get to 162 patients with lesions is probably a futile effort.

DR. SANTANA: Let me just make one last comment here. I think there is a broader issue, and it is the commitment of the investigators to the patients. If the investigators are not committed to carry out the study in the way that they designed it, they should stop the study. If they make a commitment to carry on the study, then, it should be done within the context of the research that they propose. If not, no more subjects should be submitted to this study.

DR. NERENSTONE: Just one other point in terms of numbers. We already know that every patient from the University of Pittsburgh is really a major protocol violation. It is not the same study population. You have 130 patients out of 367 who are not the same population as all the other patients.

So, those patients essentially are going to have

to be thrown out, and then whatever other accrual you have had up to this point, are you really going to be able to interpret a study where approximately a third of the patients are not really the same population?

DR. DUTCHER: So, what you are suggesting is perhaps if there is going to be a screening study, it is going to have to be amended considerably or rewritten to start over.

MR. GRUETT: Rewriting the protocol and then following it very closely I can see is a great help.

DR. DUTCHER: There was also the issue of the non-squamous patients. What was that percentage?

DR. KOBAYASHI: I don't know.

DR. GREEN: Less than 10 percent.

DR. DUTCHER: Less than 10 percent.

DR. KOBAYASHI: Less than 10 percent?

DR. DUTCHER: Or less than 10 patients?

DR. GREEN: Less than 10 percent.

DR. KOBAYASHI: I will take your word for it.

DR. D. JOHNSON: Again, though, even if that is true, I mean that should have been unquestionably exclusion criterion. A thyroid cancer patient is not the same thing as a base of tongue patient, and they were included. A lymphoma patient clearly is not the same thing. Those kinds of entry criteria need to be tightened up.

DR. GREEN: You are correct, and we have done that, and when we started this in 1994, we did go through the process that was in place at that time.

DR. DUTCHER: We think a screening study is a reasonable use of this agent, but in a different format. Even though we voted yes for continuing, I think the sentiment is really it has got to be a different study.

What about a study representing the actual recommended use?

All those who would recommend a second study?

DR. D. JOHNSON: It seems to me that is a decision the company makes. I mean I personally think that that is a reasonable study to do, but I don't know that we need to vote on whether they ought to do it or not. I guess it is up to them. I mean I am happy to vote and give them my opinion. I voted in the presidential election, too.

[Laughter.]

DR. DUTCHER: Do you recommend approval of OraTest as a diagnostic adjunct in patients with oral lesions suspected or known to be malignant, to help in detection of all sites of cancer and selection of sites to be biopsied?

DR. FORESTIERE: I would have to say no on the basis of the data that we have been presented with today.

DR. D. JOHNSON: I would agree.

DR. DUTCHER: Comment?

DR. ALBAIN: In contrast to other things that we review on this committee, I don't have the sense that this is a bad product. In fact, I have the reverse. I have the hope that it is going to be an excellent product.

I just wanted to encourage the company to hear us that way today. This is the very first time this body, an independent advisory committee to the FDA, has seen this data and heard about this drug, and we hope you take our comments as constructive, positive comments, and go back, and we hope to hear about it again. At least that is my sentiment.

DR. DUTCHER: Good. Thank you.

So, your point is that if the study is done in a way that we can interpret the information and get some answers that give us a positive result, then, it is likely to be more positive.

DR. ALBAIN: The vibes are good, not bad, that there may be something really important here.

DR. DUTCHER: Meanwhile, back to Question No. 5, do you recommend approval at this point in time?

All those who vote yes?

[No response.]

DR. DUTCHER: All those who vote no?

[Show of hands.]

DR. DUTCHER: Thirteen no.

Thank you very much.

[Whereupon, at 4:10 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

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