AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGY DRUGS ADVISORY COMMITTEE

NDA 021-801, ORPLATNA
(satraplatin capsules)
GPC Biotech Inc.

Tuesday, July 24, 2007

1:00 p.m.

ACS Conference Room, Room 1066
5630 Fishers Lane
Rockville, Maryland

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Advisory Committee Members (Voting)
- Michael Link, M.D.
- Joanne Mortimer, M.D.
- Michael Perry, M.D.
- Ronald Richardson, M.D.

Industry Representative (Non-Voting)
- Antonio Grillo-Lopez, M.D.

Temporary Voting Members
- Otis Brawley, M.D.
- William L. Dahut, M.D.
- John T. Farrar, M.D.
- Steven Krasnow, M.D.
- Pamela Haylock, R.N. (Consumer Representative)
- Wyndham Wilson, M.D.

FDA (Non-Voting)
- Richard Pazdur, M.D.
- Robert Justice, M.D.
- Martin Cohen, M.D.
- Ethan Basch, M.D., M.Sc.
- Rajeshwari Sridhara, Ph.D.
- John R. Johnson, M.D. (via telephone)

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call To Order and Introduction of the Committee

DR. ECKHARDT: Good afternoon. I would like to call the meeting to order. We are here to discuss Orplatna for the treatment of hormone refractory prostate cancer that has failed chemotherapy.

First I would like to start out with reading a statement. For topics such as those being discussed at today's meeting there are a variety of opinions, some of which are quite strongly held. Our goal at today's meeting will be a fair and open forum of discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only, only if recognized by the Chair, which is me.

We look forward to a productive meeting and I thank everybody for their participation. What I would like to do now is to go around the table with the introductions, starting with the

FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. JUSTICE: Robert Justice, Division Director, Oncology Products, FDA.

DR. COHEN: Martin Cohen, reviewer of satraplatin.

DR. BASCH: Ethan Basch, medical oncologist, Memorial Sloan-Kettering Cancer Center and guest worker, FDA.

DR. SRIDHARA: Rajeshwari Sridhara, biostatistics, FDA.

DR. BRAWLEY: Otis Brawley, medical oncologist and epidemiologist, Emory University.

DR. LINK: Michael Link, pediatric oncologist from Stanford University.

DR. PERRY: Michael Perry, medical oncologist, University of Missouri Ellis Fischel Cancer Center.

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

MS. CLIFFORD: Johanna Clifford, designated federal official to the ODAC, FDA.

DR. ECKHARDT: Gail Eckhardt, medical oncologist, University of Colorado.

DR. WILSON: Wyndham Wilson, medical oncology, NCI.

DR. MORTIMER: Joanne Mortimer, medical oncology, City of Hope.

MR. ANDERSON: Jim Anderson, patient representative. I am the Director for the Prevention of Prostate Cancer.

DR. HARRINGTON: David Harrington, statistician, Dana-Farber Cancer Institute.

MS. HAYLOCK: Pam Haylock, oncology nurse, University of Texas Medical Branch, Galveston and consumer representative.

DR. FARRAR: John Farrar, neurologist and epidemiologist with an interest in pain and symptom management and clinical trial design.

DR. DAHUT: Bill Dahut, medical oncologist, NCI.

DR. KRASNOW: Steve Krasnow, medical oncologist, VA Hospital in Washington, D.C.

DR. GRILLO-LOPEZ: I am Antonio

Grillo-Lopez. I am a hematologist/oncologist and the industry representative to this committee. I do not receive any support whatsoever from industry for my attendance to these meetings.

DR. ECKHARDT: I believe we have John Johnson participating by phone.

DR. JOHNSON: John Johnson, clinical team leader, FDA.

DR. ECKHARDT: Thank you. Now we will have the conflict of interest statement.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 USC Section 208(b)(30, full waivers have been granted to Dr. John Farrar for unrelated advisory board activities for a competing firm in which he receives less than $10,001 per year, and Dr. David Harrington for a related contract in his division from a competing firm which is funded for less than $100,000 per year.

Dr. Otis Brawley has been granted full waivers under 18 USC Section 208(b)(3) and 21 USC 355(n)(4) for his stock ownership in a competing firm which is valued from $25,001 to $50,000.

In addition, in accordance with 21 USC 355(n)(4), waivers have been granted to Pamela Haylock for her and her husband's stock ownership in a competing firm which is valued at less than $5,001, and Dr. Michael Perry for his stock ownership in three competing firms. One is values at less than $5,001 and the other two are valued at $5,001 to $25,000 per firm. Because Pamela Haylock's and Dr. Michael Perry's stock interests fall below the de minimis exception allowed under

5CFR 264202(b)(2), waivers under 18 USC 208 are not required.

Waiver documents are available at FDA's docket web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by sending a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is a retired employee of the Neoplastic Autoimmune Disease Research Institute.

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 financial involvement with any firm whose products they wish to comment upon. Thank you.

DR. ECKHARDT: We will start out with some opening remarks by Dr. Pazdur.

Opening Remarks

DR. PAZDUR: Good afternoon. The applicant is seeking an indication for satraplatin, quote, for the treatment of patients with androgen independent or hormone refractory prostate cancer that has failed prior chemotherapy, unquote.

The pivotal study for this NDA is a 950 international patient study sponsored by the applicant. A small EORTC study in 50 patients has also been submitted as a supportive study.

The primary study is a multicenter, double-blind, placebo-controlled trial enrolling patients with androgen-independent prostate cancer who have, quote, failed one, and only one, prior

chemotherapy regimen. Patients were randomized 2:1 to either satraplatin plus prednisone or placebo plus prednisone. Placebo patients were not crossed over to satraplatin after progression. The co-primary efficacy endpoints are progression-free survival, or PFS, and overall survival. Progression events were adjudicated by a blinded independent committee of radiologists and oncologists.

The FDA would like to draw the attention of the ODAC members to five major concerns regarding the application that will be highlighted in Dr. Cohen's presentation and will serve as the basis of our questions.

The first issue is the definition of one of the two co-primary endpoints, PFS. PFS is defined as a composite endpoint, consisting of radiographic progression, symptomatic progression, including pain, analgesic consumption, ECOG performance status, weight loss and other clinical events related to prostate cancer, and also skeletal-related events.

The FDA has no experience with this composite endpoint. This concern was clearly communicated to the commercial sponsor during the development phase and planning for the trial. The FDA has recommended that the trial's primary endpoint be overall survival in several meetings and correspondence with the sponsor. Although a special protocol assessment was submitted, the agency did not agree with the definition of PFS and stated that the acceptability of the sponsor-defined PFS epidemiologic would be a review issue. The acceptability of this endpoint would be subject to the evaluation of the magnitude of effect on the endpoint's component, the reliability and objectivity and the measurement of the endpoint, and the clinical significance of the claimed effect.

The FDA will seek ODAC advice on the acceptability and reliability of this composite endpoint as the basis for marketing approval. Because of the uncertainty of the acceptability and execution of this endpoint, a co-primary endpoint

of overall survival has been incorporated into the trial.

Satraplatin was better than placebo on the composite endpoint with a median PFS of 11.1 weeks versus 9.7 weeks. Satraplatin was also better than placebo on PFS defined as only radiological progression or death with a median PFS of 36.3 weeks and 20 weeks. Whether this will translate to an overall survival benefit is unknown at this time.

The second issue that we draw ODAC's attention to is that two independent radiology reviewers disagreed on progression status in 336 of the 950 patients, approximately 35 percent, requiring adjudication by a third independent radiology reader. This discrepancy raises the question whether radiographic PFS could be reliably and objective assessed in this clinical trial. The majority of radiographic progressions were based on bone scan evidence.

The third issue regards the assessment of pain progression. Note that pain progression is

both part of the composite PFS co-primary endpoint and also the basis for the secondary endpoint of time to pain progression. Because of satraplatin toxicities, it is uncertain whether blinding was maintained. Based on a review of background materials provided by the applicant describing the methods for assessing pain intensity, the FDA has determined that the single item Present Pain Intensity Scale, PPI, derived from the McGill Pain Questionnaire, has not been adequately validated for use in this study.

The PPI instrument was used a decade ago in the approval of mitoxantrone for the treatment of hormone refractory prostate cancer, but different criteria for pain response and progression were used. Also, in the mitoxantrone study the primary endpoint was reduction in pain intensity, while in the present satraplatin study the main pain endpoint is time to pain progression. Finally, the FDA Center for Drug Evaluation and Research standards for pain assessment have evolved over this interval. This protocol did not specify

any plan for pain management and progression based on increased analgesic use varied widely between countries. Non-narcotic pain medication usage was not considered in determining pain progression.

We have asked Dr. Ethan Basch, from Memorial Sloan-Kettering Cancer Center and the FDA study endpoints and labeling development group to provide a presentation on current evaluation of pain assessments and other patient-reported outcomes.

The fourth issue that we would like ODAC to consider is that only 51 percent of the patients had prior docetaxel. Docetaxel is the only drug demonstrated to improve survival in hormone refractory prostate cancer patients. This trial was started before the FDA approval of docetaxel for this indication. Subgroup analyses in patients with and without prior docetaxel show that satraplatin PFS advantage is maintained in both groups. Mature information on survival of these subgroups, however, is not available at this time.

The fifth issue is whether the FDA should

wait for final survival analysis before taking action on this application. An interim analysis of overall survival after 463 deaths does not show that Orplatna, or satraplatin, is better than placebo. The final analysis of overall survival will occur when there are 700 deaths, which is estimated to be near the end of this year.

In conclusion, the following questions will be asked to ODAC. Number one, PFS in this trial is a composite endpoint consisting of several elements. The FDA does not have experience with this endpoint. In the absence of an overall survival advantage, is PFS as defined above and noted by the sponsor an acceptable primary efficacy endpoint in this disease?

Number two, the two blinded independent radiologists had differing assessments of progression in 35 percent of the patients in the trial. Was radiographic progression reliably assessed in this trial?

Three, was pain progression reliably assess in this trial?

Lastly, as mentioned above, the interim survival analysis for this trial has a cut-off date of June 15, 2006. Satraplatin was not better than placebo on an overall survival endpoint. With a total of 632 [sic] deaths the satraplatin median survival was 61 weeks, with placebo of 57 weeks. The 700 deaths required for final analysis for survival are estimated to occur by late 2007. Please note that docetaxel showed a 2.4 month medical survival improvement in androgen independent prostate cancer patients without prior chemotherapy. And, the question that we are posing to the ODAC members is should the FDA wait for the final analysis of this randomized trial before deciding whether this application is approvable.

Thank you. I hope this highlights the areas that we would like the ODAC committee to focus on during their deliberations.

DR. ECKHARDT: All right, thank you. We will move on to the sponsor presentation, starting with Dr. Martine George.

Sponsor Presentation

Introduction to NDA 21-801: Satraplatin Capsules

DR. GEORGE: Good afternoon, Madam Chair, members of the committee, FDA and members of the audience.

[Slide]

My name is Marine George and I am head of clinical development at GPC Biotech. On behalf of my colleagues, I would like to thank you for the opt to present the satraplatin NDA.

[Slide]

Today we will discuss the findings from the pivotal Phase 3 study, the SPARC trial, in support of accelerated approval of satraplatin for the proposed indication. SPARC is a landmark study in that it is the largest study of this kind in hormone refractory prostate cancer, including almost a thousand patients. It was randomized, double-blind and placebo-controlled, and all findings were assessed by an independent centralized review committee.

[Slide]

Satraplatin is a novel agent. It is a

platinum compound. It was initially selected for clinical development because of its oral administration and its lack of cross-resistance with cisplatin. Satraplatin has also demonstrated in vitro activity against taxane resistant tumor cells.

The activity of satraplatin in hormone refractory prostate cancer was noted in early clinical trials that showed responses in patients without prior chemotherapy.

[Slide]

This slide presents the progression-free curve of the randomized EORTC trial, one of the earlier trials that compared satraplatin and prednisone to prednisone in chemotherapy-naive patients. It demonstrated a 50 percent reduction in the risk of progression. We recognize it was a small trial and that the former sponsor terminated the trial before the PFS data were available. Yet, we saw enough potential in these initial results to warrant further research.

[Slide]

So, we had substantial dialogue throughout the development of satraplatin with the US and the EU regulators, including end of Phase 2 and pre-NDA meetings and special protocol assessment, of SPA. Please note that this discussion took place about one year before the approval of the docetaxel and about three years before the issuance of the patient-reported outcomes guidance.

[Slide]

The discussions during these key regulatory meetings centered on patient eligibility, endpoints including time to tumor progression, later progression-free survival, or PFS, definitions of progression, the interim analysis and the requirements for accelerated approval. PFS, without consideration for PSA, was to be used as a primary epidemiologic to support accelerated approval of satraplatin. The agency considered PFS as used in SPARC a new composite endpoint and concluded that its use to support accelerated approval would be addressed during the review of the NDA. Please also note that the pain

assessment methodology, Present Pain Intensity and analgesic score is similar to the instrument previously validated by Tannock and colleagues in a trial used for the approval of mitoxantrone for prostate cancer. We used even more stringent criteria in the amended protocol submitted during the SPA process.

[Slide]

Satraplatin was accepted by the agency for review under Subpart H for accelerated approval with designation for priority review. Under Subpart H, the agency considers accelerated approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit such as how patients feel, function or survive. Today, we are seeking accelerated approval for satraplatin in the treatment of patients with hormone refractory prostate cancer that has failed prior chemotherapy.

[Slide]

The proposed indication is based on the results from the SPARC trial, a large, randomized

study which enrolled 950 patients. The study was double-blind and placebo-controlled, and included a review of all data by an independent committee of radiologists and medical oncologists. Progression-free was the primary endpoint for accelerated approval. That primary endpoint was met. The results were statistically highly significant and were demonstrated to be robust and consistent across the entire patient population. The safety data for the proposed label are primarily derived from SPARC, with supporting data from 29 trials involving more than 1,200 patients.

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To begin the discussion, we would like to invite Dr. Vogelzang, director of the Nevada Cancer Institute, to review the background of hormone refractory prostate cancer. Following Dr. Vogelzang, Dr. Rozencweig will present the results and conclusions from the SPARC trial. He will also share with us an analysis that addressed the questions raised in the FDA briefing document.

[Slide]

In addition, we have a number of experts who will help us address your questions.

I would now like to invite Dr. Vogelzang to the podium.

Second-Line Chemotherapy

for Hormone Refractory Prostate Cancer

DR. VOGELZANG: Thank you, Dr. George.

[Slide]

Members of ODAC and FDA, distinguished guests and those with us today whose lives have been touched by prostate cancer, my name is Nick Vogelzang. I am director of the Nevada Cancer Institute, and it is my privilege to talk to you today about a disease that I have focused on for the last 25 years, both as a practicing physician and cooperative group leader.

[Slide]

Prostate cancer is a deadly disease. With more than 27,000 deaths projected in 2007, it represents the second leading cause of cancer death in men in the United States. I can also tell you, based on the thousands of men that I have treated

and this is published experience as well, that metastatic prostate cancer disproportionately affects the bones. Indeed, over 90 percent in some studies show that patients suffer from metastatic bone disease. This leads to an exceedingly high pain burden experienced by these patients.

[Slide]

Local therapies for prostate cancer are generally highly curative. However, a subset of patients develop or present with metastatic disease. These men typically have a robust response to hormone therapy lasting two to three years, sometimes longer. Ultimately, however, virtually all of these men will see their cancer progress through hormone-based therapy. It is among these men, those with hormone refractory prostate cancer, that chemotherapy is now widely used.

[Slide]

The treatment of hormone refractory prostate cancer has improved over time with the approval of three chemotherapeutic agents.

Estramustine was approved in 1981, although its use today is quite limited. Mitoxantrone was approved in 1996 for use in combination with corticosteroids as an initial chemotherapy in the treatment of patients with pain related to advanced hormone refractory prostate cancer. Finally, docetaxel was approved in 2004 for use in combination with prednisone as a treatment for patients with androgen independent metastatic prostate cancer, and this approval was based on a large randomized clinical trial, TAX 327. Based on this registration trial and also data from SWOG 9916, docetaxel regimens now account for greater than 90 percent of chemotherapy administered in the United States for hormone refractory disease.

[Slide]

Unfortunately however, docetaxel is not a cure. In SWOG 9916, for example, we see that men receiving docetaxel had a median progression-free survival of 6.3 months. This compares to only 3.2 months for the mitoxantrone group. And, in TAX 327 PFS for every three-week docetaxel was a similar

6.7 months. These data aren't published and are quoted by permission of Dr. Mario Eisenberger.

[Slide]

Second-line chemotherapy for hormone refractory disease now becomes a focus for clinical research. It builds on a decade of investigation that established docetaxel as first-line therapy. It addresses an unmet need for a rapidly progressing and debilitating illness, one that has a median survival of approximately 12 months. It is important to note that there are no effective and well-tolerated chemotherapy regimens in this setting. In fact, less than half of these patients receive any chemotherapy.

[Slide]

Among those patients who do receive second-line chemotherapy mitoxantrone and weekly docetaxel are the most commonly used agents. However, based on a careful review of the literature, there is limited clinical evidence supporting the use of these or any other agents in the second-line setting. What remains then is an

open field for investigation. Importantly, and I need to emphasize this point, second-line regimens are now standard in other cancers, including breast, colon and lung. A second-line regimen in prostate cancer is an unmet medical need.

[Slide]

Clearly, there exist significant challenges in bringing new agents into the Phase 3 setting. In fact, many skeptics say a large multicenter Phase 3 trial in second-line prostate cancer couldn't be done. After all, it is a frail, elderly population with multiple comorbidities. Disease is rapidly progressing and debilitating, and the majority of patients suffer from difficult to measure disease with escalating bone pain. In sum, the optimal evaluation of this disease requires a composite endpoint, one that includes clinically relevant and objective measures of disease progression, pain and functional status.

[Slide]

My colleagues and I at CALGB were interested in developing such a composite endpoint,

one similar, I might add, to that which you will hear discussed today. This endpoint is composed of three widely used measures of clinical benefit including disease progression, pain control and/or analgesic use and weight loss, and/or performance status decline. We looked at nine large CALGB trials, all in first-line hormone refractory prostate cancer, and found that this intermediate endpoint was a useful predictor of survival. The median survival time among non-progressors was more than double that seen in progressors.

[Slide]

Others have looked specifically at one component of a composite endpoint, namely pain. In the CALGB database ov approximately 600 patients enrolled in three Phase 3 trials, Dr. Halabi and colleagues reported that baseline pain itself can be a useful predictor of survival. We observed a significant improvement in median survival among those with low compared to high pain at baseline.

In the TAX 327 database of 414 patients, Dr. Tannock and colleagues observed that a pain

response predicted for near doubling of the median survival.

Unfortunately, until now there have been no studies of baseline pain or pain response in patients undergoing second-line chemotherapy.

[Slide]

I have been caring for men with hormone refractory prostate cancer for many years. These men are often debilitated and face excruciating pain. This is well demonstrated in survey data presented by Dr. Moyad at last year's ASCO meeting. They interviewed 409 men with hormone refractory prostate cancer. Of these men, 60 percent experienced pain every day; 50 percent reported that pain interfered with their activities; 47 percent reported requiring daily pain medicine; and nearly a third suffered depression related to their pain. These patients clearly need new and well tolerated therapies that will slow the course of their disease, reduce pain and improve the quality of their life.

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In summary, hormone refractory prostate cancer progressing after first-line chemotherapy represents an unmet medical need. This is a rapidly advancing, debilitating, and ultimately fatal disease. Those of us who treat these patients and, indeed, the patients themselves urgently need effective and well tolerated therapies.

Finally, the optimal clinical evaluation of this disease requires, in fact it demands a composite endpoint that includes measures of pain response and tumor progression.

Thank you very much for your attention. Let me now turn the podium over to my colleague, Dr. Rozencweig.

Efficacy and Safety of Satraplatin: SPARC Trial

DR. ROZENCWEIG: Thank you, Dr. Vogelzang.

[Slide]

Good afternoon. My name is Marcel Rozencweig. I am the chief medical officer at GPC Biotech.

[Slide]

In this presentation I will review the design and the results of the SPARC trial or registration trial. In the second part of the presentation I will also address questions raised by the agency in their briefing document.

[Slide]

SPARC was a double-blind, placebo-controlled trial. The trial was designed for patients with hormone resistant prostate cancer. These patients had distant metastasises and had failed at least two courses of one prior chemotherapy. Patients were randomized in a 2:1 ratio after stratification by performance status, PPI score and the type of progressive disease with first-line chemotherapy. Satraplatin was given orally at a daily dose of 80 mg/m^2 daily for five consecutive days in cycles repeated every five weeks. All patients in both arms received prednisone 5 mg BID continuously. Only those patients in the satraplatin group received prophylactic granisetron. In the placebo group the patients received placebo antiemetic prophylaxis.

[Slide]

We used progression-free survival for accelerated approval in a trial powered for survival. Both progression-free survival and overall survival were treated as primary endpoints, the first for accelerated approval, and overall survival for full approval. Time to pain progression was a secondary endpoint. The statistical plan also included a number of additional endpoints, including pain response, tumor response according to the RECIST criteria and PSA decline according to the Bubley criteria.

[Slide]

Progression-free survival and overall survival were assessed by the Kaplan-Meier method. Treatments were compared using a two-sided log-rank test stratified by performance status, PPI score and type of progression at entry. The overall alpha was set at 0.05 and it was equally split between PFS and OS. This analysis was conducted on an intent-to-treat basis unless otherwise indicated, and all randomized patients

are accounted for. The target accrual was 912 patients and for the final analysis of PFS about 700 events were required to show a hazard ratio of 0.77 with a power of 90 percent. The same requirements applied to the final analysis of overall survival.

[Slide]

The PFS endpoint was designed as a composite endpoint to account fo the wide variety of presentations and outcomes in this disease. We came up with that composite endpoint after long discussions with many experts in the field. It included criteria of clinical relevance that have been used individually or in various combinations in prior trials. So, PFS was defined as the time from randomization to the first occurrence of any of the following: Radiographic progression and, in the case of bone scans, at least two new lesions were required; Symptomatic progression based on pain; performance status or weight loss; skeletal-related events; intervention for disease-related obstruction of the GU tract or

death from any cause. I should note that an isolated PSA elevation was not considered as a PFS event in this study.

[Slide]

Pain assessment was derived from methods established in previous trials. The patients were asked to report their average pain over 24 hours as has been done for the mitoxantrone submission. They had to complete a highly detailed disease-related pain diary that included a PPI numeric score using the six-point scale from McGill-Melzack, and the number, types and doses of their daily analgesics. The analgesic scores were based solely on the use of narcotics and were normalized to a standard dose of morphine. The weekly average PPI scores and the weekly average analgesic scores were calculated centrally in a blinded fashion, and reviewed as such by the independent review committee.

[Slide]

Pain progression criteria were derived from the mitoxantrone registration trial in HRPC.

The criteria for SPARC were modified and made more stringent. The assessments were done continuously in SPARC instead of once every three weeks as done in the mitoxantrone trial. Changes in PPI in SPARC had to be sustained for a minimum of two weeks instead of a confirmation on a single day at least three weeks apart. And, if anything, SPARC used a higher hurdle regarding the definition of progression and increased use of non-narcotics was not considered sufficient to qualify as progression in this study.

[Slide]

SPARC was certainly not the first study to use an independent review committee to adjudicate progression events. However, we did go to new extremes to ensure blinding of the IRC process. The IRC assessed the type of PFS events and assigned the earliest day of progression. The IRC process consisted of a central blinded radiology review of all scans and all x-rays, and this was followed by a central blinded oncology review of all 950 cases. Note that the IRC had no access to

blood counts, no access for the most part to PSA values, and no access at all to investigator assessment of progression.

[Slide]

A total of 950 patients were randomized over a two-year period. SPARC was an international study and this was a huge undertaking. It included patients from 170 centers in 16 countries. Most patients came from the U.S., France and Argentina. Importantly, the ten largest centers accounted for only 22 percent of the total accrual so our results were certainly not driven by a small number of centers.

[Slide]

Overall, the two treatment groups were well balanced in terms of pre-treatment characteristics. The details are contained in the briefing document of the sponsor. Note that 51 percent of the patients had received docetaxel, an important observation considering that docetaxel is now known to prolong survival as first-line chemotherapy in this disease.

[Slide]

Let me now go to the efficacy data from SPARC.

[Slide]

At the time of the data cut-off we had 802 PFS events. These are the results of the progression-free survival of the disease. As you can see, overall there was a highly significant difference that favored the satraplatin group. The hazard ratio was 0.67 and the stratified log-rank p value was less than 10^{-4}. At the median the difference is only 1.4 weeks but the median doesn't tell the whole story. It certainly does not describe entirely the curve. The curves are largely skewed to the right. Beginning at week 10 there is a clear separation between the two groups. The proportion of patients alive and free of progression at six months is 30 percent with satraplatin, 16 percent with the control. At 12 months the corresponding figures are 17 percent and 7 percent respectively.

[Slide]

Radiographic events and pain progression were the main drivers of the PFS outcome in those arms. They account for more than 70 percent of all the PFS events.

[Slide]

These are the PFS curves for the subset of patients who received prior docetaxel. This is a key subset. These are the patients who failed the current standard of care. And, we see that satraplatin is as active in this situation as in the entire intent-to-treat population. There was a highly significant benefit favoring satraplatin. As you can see, the hazard ratio is 0.67 and the stratified log-rank p value is 0.0006.

[Slide]

We have also looked at PFS in other prespecified subsets and the results again are remarkably consistent. This is true whether the data are analyzed by stratification factors, age, key prognostic categories including those defined by anemia, LDH, alkaline phosphatase, and also ethnicity or geographic region. As you see, all of

the hazard ratios represented here favor satraplatin, and the difference was significant in nearly all subsets.

[Slide]

As we noted earlier, time to progression was secondary endpoint. It was defined as the time from randomization to the first pain-related progression. Here we see a forest plot for the entire ITT population, as well as all of the prespecified subsets. Once again, the results favor satraplatin in all these analyses. All of these hazard ratios and for most subsets also the 95 percent confidence intervals reside entirely on the side favoring satraplatin.

[Slide]

Pain response was defined as a reduction in PPI score by at least two points relative to baseline, with no increase in analgesic score. By definition, these responses had to last for a minimum of five weeks in contrast, I might say, to the three weeks required in the mitoxantrone registration trial. But even with this most

stringent criteria, the pain response rate observed here was almost twice as high in the satraplatin arm as compared to placebo, 24 percent versus 13 percent, and this difference is highly significant.

[Slide]

We have also conducted several analyses to better understand the pain palliation achieved with satraplatin. Specifically, more patients in the satraplatin arm became pain-free for a minimum of five weeks, and this was particularly evident when one looks at those patients with a higher PPI score at baseline. Furthermore, more patients in the satraplatin arm demonstrated a 50 percent reduction in narcotic use for a minimum of five weeks, and this too was especially evident among patients with a higher baseline analgesic score.

[Slide]

In this analysis we looked at the proportion of patients with a reduction in PPI score of at least 50 percent relative to baseline, and this was done on a weekly basis. These two curves again show a significant benefit associated

with satraplatin. We have an odds ratio here of about 2. Note also that this effect was already present within the first ten weeks. This is a very early benefit that we observed here.

[Slide]

This is the PSA response using the Bubley criteria and tumor response using the RECIST criteria. Consistent with all the other data, there is a significantly higher response rate with both metrics, again, favoring the satraplatin arm in a highly significant fashion.

[Slide]

At this juncture we have only an interim analysis of overall survival. We see that the hazard ratio favors the satraplatin arm but there is no difference of statistical significance in this interim analysis. This interim analysis is based on 463 deaths. The final analysis is pending the prespecified number of events. Please recall that the accelerated approval we are seeking today is based on PFS. We are planning to discuss overall survival with the agency when seeking full

approval at a later date.

[Slide]

Let me now briefly review the safety data.

[Slide]

Myelosuppression was the most frequent adverse event seen with satraplatin. Here we have tabulated grade 3 and 4 hematology adverse events, and we observe higher rates of neutropenia, thrombocytopenia, leukopenia and anemia. However, the percent of patients experiencing these toxicities was relatively low and, most notably, grade 4 myelosuppression was found in only four percent or less of these patients.

[Slide]

In this table we see that satraplatin was relatively well tolerated. The table summarizes the non-hematologic clinical adverse events that were more frequent with satraplatin than control when all grades of severity are analyzed. This included mostly GI manifestations, fatigue and infection.

We also performed a conservative

retrospective analysis of pooled events which indicate a higher rate of fever, bleeding, pulmonary events and thrombosis. Note, however, that few of these differences remain significant when only grade 3 and 4 events were compared. These are highlighted in the table. Note also that the incidence of grace 3 and 4 adverse events was under five percent in all these cases. Of particular interest, there was no neuropathy and no renal toxicity associated with satraplatin therapy.

[Slide]

In summary, we believe that the data from the SPARC trial provides evidence to support the efficacy and the safety of satraplatin as second-line therapy for hormone refractory prostate cancer. Specifically, the primary PFS endpoint was achieved with robust results, supported by a myriad of sensitivity analyses. And, these data are of clinical relevance. The PFS results were primarily and equally driven by tumor progression and pain progression. Delaying the progression of disease in this setting is clinically meaningful. The

significant benefit of satraplatin was highly consistent across all of the prespecified sensitivity and subset analyses, especially with regard to the type of prior chemotherapy.

[Slide]

We see positive outcomes associated with satraplatin also in terms of delay in pain progression, pain response, PSA response and objective tumor response.

[Slide]

The safety profile of satraplatin, again, is well established. The drug is well tolerated. In this elderly population with very advanced disease satraplatin offers the possibility of a new chemotherapy option and it is easy to administer.

Myelosuppression and GI manifestations were the most frequently observed adverse events, but these adverse events were mostly mild to moderate and generally easy to manage.

[Slide]

With the remaining time, let me turn my attention to the briefing document provided by the

agency. Several concerns have been raised and I would like to address them one by one.

[Slide]

Topic number one, the FDA has no experience with the composite endpoint employed in our registration trial. There is experience with the individual components and combinations of these components but not with all components used together.

As you review this application, keep in mind that all of the components in our composite endpoint are of clinical relevance. As you will recall from Dr. Vogelzang's presentation, pain outcomes are associated with survival. Keep also in mind that the results of SPARC are statistically very persuasive and extraordinarily consistent. The differences that we observed persisted regardless of how the data were analyzed or re-analyzed.

[Slide]

The second question concerns the central radiology review. The IRC process that we have

designed is absolutely state-of-the-art and is now a standard for the industry. Please note that the threshold for adjudication was extremely low. As little as one-day difference between readers was enough to send the case for central adjudication.

The agency questions our rate of adjudication, but I think that this should be considered in context. There were about 3,000 time points analyzed and there were about 7,000 radiographic assessments.

[Slide]

Here we see the numbers that are in dispute. We had originally, in the briefing document, 367 patients. This has been reduced since. I will go over this in a moment. You can see that from the original 367 cases of disagreement in the briefing document, in fact, 166 have no impact on the PFS event, mostly because there was an earlier non-radiographic PFS event that occurred in 116 patients. There was a disagreement on RECIST response in 31 criteria and the Division has agreed to delete these 31 cases

from the total. There was also small disagreement that concerned differences of less than seven days in 19 patients. This was considered inconsequential in our estimate. Note that the region here is about two days among these 19 patients.

So, we are left with 201 patients in whom disagreement between readers could have had a potential impact on the PFS. But, in fact, they don't change our conclusions.

[Slide]

In response to this concern, we have re-analyzed the radiographic data using a worst-case scenario. Specifically, we used the earlier of the progression dates for satraplatin and the later of the progression dates for the control group. As you can see, the difference in PFS retains its statistical significance in favor of satraplatin even under this worst-case scenario. This is a standard, I might add, that has not always been achieved in recent submissions of other oncology drugs that were ultimately approved.

[Slide]

Topic number three, the FDA standards changed after the initiation of SPARC, but pain assessments in our trial are still aligned with the new draft guidance. We have shown retrospectively that these pain assessments are consistent with current psychometric standards. They are able to measure clinically meaningful differences, and there is minimal influence of language and culture.

[Slide]

According to the updated draft guidance, a one-item PRO instrument to measure pain severity is acceptable as long as it is reliable and valid. Let me first show you that our PPI score is, in fact, a one-item pain measure.

[Slide]

This is an example of a diary used in the SPARC trial. The pain scores are entered by the patient here, at the bottom, as a single numeric value on a daily basis. So, this is a single-item measure reported by the patients and confer consistency and inter-rater reliability are not

applicable here.

[Slide]

To test the reliability of the PPI score, we have compared the individual PPI values at baseline and at week one. We have also done this between week one and week two, and the results are the same. In this test/retest analysis there is a strong correlation that is highly significant and, therefore, I think we can conclude that this score is reliable and reproducible.

An acceptable approach to define a meaningful change in pain scales is based on standard deviations. One half of a standard deviation is considered to be a meaningful change. Accordingly, in our study, based on the standard deviation of the PPI scores at baseline, it actually appears that the one-unit change in the PPI score reflects clinically significant pain progression.

[Slide]

We have also found that there is no substantive effect of culture, language or region

on the PPI. This conclusion is based on the linear effects model of within patient variation. In this model and in our analysis the region effect accounted for less than one percent of the variation; the country for 1.2 percent; and the site for less than five percent.

[Slide]

We have carried out a number of sensitivity analyses to further substantiate the clinical significance of the SPARC pain measures. Here we see a landmark analysis at week five. This is an analysis for survival as a function of the PPI score after one cycle of therapy. At that time, satraplatin has had a chance to exert at least some anti-tumor activity. The data show that PPI is a discriminant for survival and the difference between these PPI groups is highly significant.

[Slide]

This is a landmark analysis at three months, and this analysis demonstrates that the survival in pain responders is prolonged as

compared to non-responders and the difference, again, is highly significant.

[Slide]

Here we show an association between pain progression and bone progression. Among patients who had adequate follow-up data we see that more than 70 percent of the patients who had pain progression eventually also had bone progression, and this observation further highlights the clinical significance of pain progression in our study.

[Slide]

The agency suggested that the blinding in SPARC may not have been maintained because of satraplatin adverse reactions. I think this is a legitimate concern in a chemotherapy trial, but we believe that this was not an issue in this study. As can be seen here with the point estimates of the hazard ratios, PFS favors satraplatin regardless of the presence or absence of significant myelosuppression or gastrointestinal manifestations, which were the most frequent

adverse events observed in the study.

[Slide]

The agency also questioned the fact that non-narcotics were used as pain medication in our trial. However, the inclusion of non-narcotics in our analgesic scores would not have changed the results. As shown in this slide, pain response outcomes remained significantly better with satraplatin even when we exclude patients who started NSAIDs on study.

[Slide]

Finally, as can be seen in this sensitivity analysis, PFS remained significant and similar to the ITT population even if all of the pain progression data are excluded from the analysis.

[Slide]

The first topic raised by the agency in the briefing document relates to the fact that only 51 percent of the patients received docetaxel. Let me first remind you that docetaxel was approved for HRPC nine months after the first patient was

entered in the SPARC trial. In all of our analyses, every single one, the results were the same with or without prior docetaxel. In the United States, about 90 percent or more of the patients with HRPC currently receive fist-line chemotherapy with docetaxel. Our claim for second-line is actually a claim for treatment following failure of the current standard of care.

[Slide]

Should FDA wait for the final survival analysis before taking action? First, let us not forget that accelerated approval was created to make drugs available on the basis of reasonable and preliminary evidence. We had originally anticipated to have all of the survival events before the end of the year, but the event rate is substantially slowing down and we will have to wait much longer than we thought for the final analysis of survival and, obviously, we will have to wait even longer for approval. This is now unlikely to occur within the next 12 months.

Please consider the following when

thinking about this last question: We are talking about a huge unmet medical need with a painful and debilitating disease, and I will remind you that SPARC is the first and only study of its size that is addressing this unmet medical need.

There is no question that satraplatin works. There is evidence of disease control; there is evidence of symptom control, and there is evidence of safety. And, this evidence supports that satraplatin should be made available to patients as rapidly as possible.

[Slide]

The treatment of advance prostate cancer is a tremendous challenge. Developing drugs in this setting is also a tremendous challenge. The data we presented today demonstrate beyond any doubt that satraplatin provides meaningful benefit to these patients. We strongly believe that the data presented today are adequate to support accelerated approval in second-line chemotherapy for the treatment of patients with hormone refractory prostate cancer.

Finally, on behalf of all my colleagues, let me thank all those who contributed to the SPARC trial, specifically the patients, their families and the investigators who contributed to the trial. I also thank you for your time and your attention.

DR. ECKHARDT: Thank you. Now we will move on to the FDA presentation. Dr. Cohen?

FDA Presentation

Clinical Review

DR. COHEN: Good afternoon. My name is Martin Cohen and I will present the FDA review of the satraplatin application. First a housekeeping question, can you hear me?

[Slide]

The NDA that we are discussing is NDA 21-801. The drug, as you know, is satraplatin, an orally administered organoplatinum compound. The proposed indication is for the treatment of patients with hormone refractory prostate cancer who have failed prior therapy.

[Slide]

As mentioned, the study population was

hormone refractory metastatic prostate cancer. Patients were enrolled after failure of one prior chemotherapy regimen that did not include a platinum drug. They were ambulatory, with an ECOG performance status of less than or equal to 2, and they were on a stable analgesic regimen.

[Slide]

The study, as you have heard, was a double-blind, randomized trial that compared treatment with satraplatin plus prednisone versus placebo plus prednisone. Satraplatin was given orally at a dose of 80 mg/m^2 daily for five days every 35 days, and prednisone was given at a dose of 5 mg twice daily throughout the treatment period. Randomization was 2:1 in favor of the satraplatin arm. Prior to randomization patients were stratified by performance status 0 or 1 versus 2, baseline present pain intensity, or PPI, score of 0 or 1 versus 2-5 and type of progression on prior chemotherapy. That is, whether it was due to an increase in tumor size or to a rising PSA. If both tumor size and PSA increased progression was

attributed to increase size.

[Slide]

The study endpoints are listed on this slide. The co-primary endpoints were progression-free survival and overall survival. A secondary endpoint was time to pain progression. The study cut-off date for efficacy analyses was June 15, 2006. As will be seen on the next slide, PFS is a composite endpoint. This endpoint has not been used previously in any registration trial submitted to the FDA. The FDA strongly recommended that survival should be the primary endpoint and the study was, in fact, powered for survival.

[Slide]

As stated, progression-free was a composite endpoint that included radiologic progression; pain progression; a rise in ECOG performance status or two units; a greater than 10 percent weight loss; the occurrence of skeletal related events including pathologic bone fracture, radiation therapy or surgery to bone, spinal cord or nerveroot compression or start of bisphosphonate

therapy in response to new bone pain. Clinical events included initiation of new antineoplastic therapy and the occurrence of obstructive events such as urethral or bladder obstruction. Death prior to progression was a final element of the PFS definition.

[Slide]

This slide shows some of the meetings FDA had with the sponsor concerning the proposed PFS endpoint. In all of the meetings FDA stressed that it had no prior experience with the composite endpoint and, more specifically, with the pain performance status and weight loss components of the definition. In prior applications pain palliation was evaluated. In this application pain progression was evaluated. Since all components of a composite endpoint should have equal clinical significance, the FDA raised the issue as to whether 10 percent weight loss, a two-point decline in ECOG performance status, the start of bisphosphonate therapy for bone pain and investigator starting new chemotherapy before

progression, or a less than or equal to 25 percent increase in pain medication was of equal significance to objective tumor growth.

In addition, since all of the components of a composite endpoint should have equal clinical significance, it follows that there should be adequate numbers of patients to evaluate each component of the composite endpoint.

The sponsor's definition of progression-free survival leads the initial question that we will ask ODAC to consider as stated on the next slide.

[Slide]

That question is, is the composite endpoint, as defined, an appropriate endpoint for treatment evaluation in hormone refractory prostate cancer? Information relevant to this question will be presented in the clinical results portion of this presentation.

[Slide]

Another regulatory concern relates to sample size. When the study was submitted in May,

2003 overall survival was the primary endpoint. To detect the hazard ratio of 1.3 with 80 percent power required 792 patients. In the July, 2003 submission power was increased to 85 percent and 912 patients wee required. Final analysis of progression-free survival and overall survival was to occur after 837 events and 602 events respectively.

A submission in April, 2004 has similar sample size considerations as the July, 2003 submission. In June, 2005 PFS and overall survival were co-primary endpoints. The power was 90 percent. Final analysis was to be done after 694 progression-free survival events and 700 overall survival events. And, 950 patients were enrolled and there were 802 progressions, instead of the planned 694 events.

In conclusion, it appears that the study is somewhat overpowered. As a result, small differences in outcomes that are statistically significant may not be clinically meaningful.

[Slide]

This study was carried out in 16 countries. The United States and France were the two largest participants, enrolling 258 and 141 of the total 950 study patients. The next largest participants were Argentina with 98 patients and the United Kingdom with 85.

[Slide]

Patient demographics are shown on this slide. The two treatment groups were well balanced for all the demographic characteristics and only the total for the two groups is shown on this slide. As expected, study patients were elderly. The median age was 70 years, with a range from 42 to 95 years. Most patients were Caucasian and most were ambulatory, with an ECOG performance status of 0 or 1. Thirty percent were receiving bisphosphonates; 36 percent had no pain or a Present Pain Intensity score of 0; 41 percent were taking no narcotic analgesics; and 51 percent had received prior docetaxel treatment and, again, as was adequately stated previously, docetaxel was the only drug shown to improve survival in patients

with hormone refractory prostate cancer.

[Slide]

Turning now to efficacy results as submitted by the sponsor to the FDA, progression-free survival results are shown on this slide. The black curve is satraplatin plus prednisone and the red is prednisone alone. As you have heard, median progression-free survival was 11.1 weeks on satraplatin plus prednisone and 9.7 weeks for the control group, prednisone alone.

While statistical significance in favor of the satraplatin arm was demonstrated, as will be pointed out, ODAC will have to consider as to whether or not these results are clinically meaningful. As with the overall progression-free survival analysis, numerous subgroup analyses were performed and in nearly all, including whether or not the patient had received prior docetaxel, the satraplatin arm gave statistically superior results. Again, ODAC will have to consider as to whether or not these results are clinically meaningful.

[Slide]

The sponsor's interim analysis of overall survival is shown on this slide. As of the cut-off date of June 15th, 2006, there were 463 death events or 66 percent of the planned 700 deaths. Median survival was 61.3 weeks and 57.3 weeks on the satraplatin and placebo arms respectively. The stratified log-rank p value was 0.388.

[Slide]

This gives our next ODAC question, should the FDA wait for the final survival analysis before deciding whether or not this application is approvable?

[Slide]

Turning now to progression-free survival results, as previously stated, PFS was the sponsor's choice for the primary efficacy endpoint. PFS events, as defined by the sponsor, are shown ob this slide. Progression occurred in 802 or 950 study patients, 528 on the satraplatin arm and 274 on the control arm. Progression based on radiologic studies, including x-rays, CT scans, MRI

exams and bone scans, accounted for 36 percent of the total progression events, while progression based on increased pain or increased analgesic use occurred in 37 percent. Death in the absence of progression accounted for eight percent of events, while progression based on increase in performance status or greater than 10 percent weight loss accounted for six percent and other progressions, including skeletal-related events, new chemotherapy or clinical progression, accounted for the remaining 13 percent.

Because the majority of the progression events involved radiologic and pain progression, and because issues arose when FDA analyzed this data, the next few slides will discuss radiologic and pain progression in detail.

[Slide]

Radiologic progression was determined in the following manner, all radiologic studies were reviewed independently by two radiologists who were blinded as to treatment assignment. If the two radiologists disagreed as to whether or outcome

progression had occurred or if they were in agreement that progression had occurred but they disagreed as to the date of progression, a third radiologist adjudicated and supported the view of one or the other primary radiologist.

[Slide]

This slide reviews adjudicated radiologic progressions. As noted, there were 290 progressions based on radiology studies. Of these, 116 or 40 percent required adjudication. Similarly, for the 660 patients who were ultimately considered not to have radiologic progression, 220 or 33 percent were adjudicated. In total, therefore, of 950 study patients, 336 or 35 percent required adjudication. The need for adjudication and the uncertainty as to whether the adjudicator's judgment was correct makes data on radiologic progression suspect.

[Slide]

This raises the next ODAC question, namely, what does the fact that 336 of 950 study patients, or 35 percent, required adjudication to

determine progression indicate about the reliability of radiologic progression assessment?

[Slide]

In raising questions about the reliability of radiologic progression data, it is useful to consider the imaging method used to detect radiologic progression. Again, there were a total of 290 radiologic progressions, of which 40 percent were adjudicated. Of the 290 radiologic progressions, 66 percent were detected by bone scan only and an additional 16 percent of the progressions were detected by bone scan along with CT, MRI or x-ray examination. Overall, therefore, 82 percent of radiologic progressions required evaluation of bone scans. This data indicates that bone scan evaluation is difficult even for experienced radiologists.

[Slide]

Since 16 countries participated in the trial, it is of interest to look at radiologic progression by country. In this slide Canada is excluded since only three patients were enrolled in

Canada. As previously noted, radiologic progression occurred overall in 36 percent of patients. As summarized in this slide, there did not seem to be great disparity in radiologic progression among countries, with a range of 25 percent radiologic progression in the United Kingdom, which is the grey bar, to 46 percent in Croatia, which is the light blue bar toward the center. Radiologic progression for the United States and France, the two largest contributors, seen on the far left of the chart, was 28 percent and 27 percent respectively.

[Slide]

Turning now to pain progression, the sponsor analysis of time to pain progression, a secondary efficacy endpoint, is shown on this slide. As previously, the satraplatin arm is in black and the prednisone arm in red. Again, the satraplatin arm resulted in a statistically significant but clinically questionable, for reasons to be subsequently discussed, delay in pain progression.

[Slide]

Pain progression assessment was based on average weekly Present Pain Intensity, or PPI, score by average narcotic analgesic consumption as recorded by patients in a pain diary. The PPI score consisted of six pain categories, ranging from no pain to excruciating pain. All pain diaries were reviewed blindly by two independent reviewers.

Pain progression was defined as an increase in cancer-related pain of at least one point from baseline or at least two points from the nadir observed for at least two consecutive weeks, or an increase in the average analgesic score of greater than 25 percent compared with baseline also observed for two consecutive weeks. Average analgesic score was based entirely on narcotic use. Non-narcotic analgesic use was not evaluated. Patients who had an analgesic score of zero at baseline, indicating that they were taking no narcotics, were considered to have pain progression if they subsequently started narcotics at any dose

and schedule and had an average weekly score of greater than zero for at least two consecutive weeks.

I am going to present initial comments on the issue of pain progression. A more detailed discussion by Dr. Ethan Basch of the study endpoints and label development group will follow my talk.

[Slide]

Patients in the present study were remarkably pain-free. Baseline Present Pain Intensity of study patients is shown on this slide using the six-point pain assessment score. As seen, 36 percent of study patients had no pain or a PPI score of 0; 28 percent had mild pain or a PPI score of 1; and 23 percent had discomforting pain or a PPI score of 2.

[Slide]

This slide shows baseline narcotic use. Of the 327 patients with no pain or a PPI equal to zero, 92 percent were not on narcotics. Similarly, for the 258 patients with mild or PPI 1 baseline

pain, 62 percent were not on narcotics. For the 212 patients with discomforting pain or PPI 2, 33 percent were not on narcotics.

Because many patients had no pain or only mild pain, and because non-narcotic analgesics were not evaluated as part of the analgesic regimen, it is possible that the variable use of non-narcotic analgesics to control mild pain in the various study countries could have confounded the evaluation of pain progression. Also, as will be seen on subsequent slides, narcotic administration at any dose or frequency, such that the average weekly narcotic analgesic score was greater than zero for two consecutive constituted pain progression.

[Slide]

As previously mentioned, 16 countries participated in this trial. Canada is excluded from this chart, having enrolled only three patients. The fact that 16 different countries participate in the study raises technical issues regarding translation and cultural adaptation,

content validity and construct validity of the pain questionnaire. An additional issue with pain evaluation might also relate to different philosophies of pain management in the different countries.

While the percent of patients with radiologic progression is relatively similar from country to country, the percent of patients with progression based on pain and/or analgesic use is more variable. Only five percent of 22 Hungarian study patients and only 17 percent of 42 Spanish study patients had pain progression, as seen on the far right of the slide, whereas for the United States and France, the two countries enrolling the largest number of patients, pain progression occurred in 40 percent and 34 percent of patients respectively, as seen on the far left of the slide.

[Slide]

This slide shows analgesic score progression as a percent of all pain progressions. It might be expected that there would be more progressions based on increased analgesic

consumption than on increased unrelieved pain since physicians would likely either provide more potent analgesics or prescribe more breakthrough medication rather than leave a patient with untreated increased pain.

Study results from 14 countries, excluding Hungary and Canada because of small numbers of patients, demonstrate that the majority of pain progressions were because of increased analgesic use in eight countries, and almost 50 percent in two countries, namely Croatia and Peru. In the remaining four countries, namely Poland, Italy, Germany and Russia, only about one-third of pain progressions were based on increased analgesic use.

Since non-narcotic drugs might be expected to relieve pain for many patients with mild pain and for some patients with discomforting pain, it is possible that some of the variability noted in this slide is due to initial treatment with non-narcotic drugs rather than we more potent narcotic treatment. Similarly, for patients not taking narcotics at baseline, any narcotic

administration such that the average weekly analgesic score was greater than zero, constituted pain progression. These factors might confound time to pain progression.

[Slide]

The pain progression portion of the progression-free survival epidemiologic leads to the following ODAC discussion item. That is, based on the data that I have presented and on the information that Dr. Basch will present in the following presentation, this question concerns whether pain progression was reliably assessed in the trial.

[Slide]

Objective response rate is shown on this slide. There were 274 satraplatin treated patients and 134 prednisone alone treated patients who had soft tissue lesions evaluable for response. The objective response rate was 8 percent versus 0.7 percent in favor of the satraplatin arm. Thirty-one patients had adjudication to determine response status.

[Slide]

Turning now drug exposure a summarized on this slide, patients in the satraplatin group had a median of four cycles of treatment versus two cycles for the placebo group, with a median duration of treatment of 20.4 weeks for satraplatin plus prednisone and 10.3 weeks for prednisone plus placebo. As expected, dose reductions and dose delays in treatment occurred more frequently in the satraplatin arm. The satraplatin or placebo group was increased in about 10 percent of patients. The observation that considerably more satraplatin treated patients than placebo treated patients had dose reductions or treatment delays raises the question as to whether treatment blinding could be maintained.

[Slide]

Hematologic toxicity during cycle one of treatment is shown on this slide. Satraplatin treatment is associated with myelosuppression, primarily thrombocytopenia and neutropenia. Myelosuppression was the primary reason for

satraplatin dosage reductions. There were also more red blood cell and platelet transfusions in the satraplatin arm than the placebo arm. Red blood cell transfusions were given to 16 percent of satraplatin patients versus 8 percent of placebo patients, and platelet transfusions to 4 percent versus 0.3 percent respectfully. Again, the higher frequency of thrombocytopenia and neutropenia in satraplatin treated patients raises the question about whether blinding can be maintained.

[Slide]

Individual grade 3/4 and non-hematologic treatment emergent adverse events with a significantly higher incidence in the satraplatin group compared to the placebo group are shown on this slide. Satraplatin plus prednisone treated patients were more likely to have grade 3/4 TEAEs than were placebo plus prednisone treated patients, 55 percent versus 30 percent. Gastrointestinal disorders occurring significantly more frequently in satraplatin treated patients were diarrhea and vomiting.

Considering that patients in the satraplatin group had a median of four cycles of treatment versus two cycles in the placebo group, non-hematologic TEAEs also were examined as a percentage of cycles. Results were similar as those observed on a per patient basis, with a significantly higher incidence of gastrointestinal disorders, including diarrhea and vomiting, in the satraplatin group. There were 14 cases of treatment emergent renal failure in the satraplatin group compared to two cases in the placebo group. For most of these cases, however, there was evidence of renal impairment at baseline.

[Slide]

To summarize the four questions that we will ask ODAC to consider include, is progression-free, as defined, an acceptable basis for treatment evaluation in hormone refractory prostate cancer? Was radiologic progression reliably assessed? Was pain progression reliably assessed? And, should the FDA wait for the final survival analysis before deciding whether this

application is approvable? We were led to believe that that analysis would be available toward the end of 2007. Thank you.

DR. ECKHARDT: Next we are going to have a presentation by Dr. Ethan Basch.

Methods Used to Assess and Report Pain-Related Endpoints

[Slide]

DR. BASCH: I will be discussing the method used for assessment for pain-related endpoints in NDA 21-801.

[Slide]

By way of introduction, I am a medical oncologist and an outcomes researcher at Memorial Sloan-Kettering Center where I clinically focus on prostate cancer and I conduct research on patient-reported outcomes. I am here today in my ongoing role as a guest worker in the FDA study endpoints and label development team of the Office of New Drugs. I receive research funding from the NCI, ASCO, Department of Defense and New York State. I receive no pharmaceutical industry

funding and have no financial interest in any commercial entities relevant to this application.

[Slide]

Pain is an important endpoint in metastatic prostate cancer, and has been the basis for labeling claims in the past. Pain measurement is methodologically challenging and, while there is no single gold standard approach, standard methods have evolved over time to guide the development, administration and analysis of pain endpoints in clinical trials. In order to assist sponsors with the difficult tasks of identifying, developing and implementing endpoints which appear to be standards, in February, 2006 the FDA issued a draft guidance on the use of patient-reported outcome measures including pain. Notably, this guidance reflects FDA's current thinking based upon standards for assessment of patient-reported outcomes that already existed prior to the development of the guidance.

[Slide]

The proposed claim in this application is

progression-free survival which is based upon a composite endpoint designed by the sponsor which has not been used in past NDAs. Therefore, the FDA has no prior experience with this endpoint model. To meet PFS criteria for progression in this model patients could experience radiographic progression or skeletal-related events or symptomatic progression. This third criterion, symptomatic progression, is itself a composite endpoint, consisting of four subcomponents, the fourth of which is pain progression. Pain progression is also itself a composite endpoint consisting of either an increased score in a single question called the Present Pain Intensity or PPI item, or increased opioid use.

The key point here is that a change in any one of these components or subcomponents could yield a positive finding causing a patient to meet the PFS primary endpoint. It is, therefore, germane to understand how each of these criteria was developed, captured and analyzed. I will be focusing primarily on the pain-related endpoints.

[Slide]

The proposed claim is based on the results of a randomized, controlled trial of satraplatin plus prednisone versus placebo plus prednisone as second-line chemotherapy.

[Slide]

As previously shown in the sponsor presentation, in this trial PPI pain intensity scores and opioid doses were self-reported by patients daily using the paper form shown on this slide. In the upper grid the name of opioids and daily doses were entered. In the lower grid PPI pain intensity scores were entered based on instructions I will describe shortly.

[Slide]

The PPI is a single question which was plucked from a longer questionnaire, the McGill Pain Questionnaire, which was developed in the 1970s. The sponsor notes that the PPI question was used in the approval of mitoxantrone for metastatic prostate cancer more than a decade ago.

[Slide]

The PPI question, as used in the satraplatin study, asked patients to report their average pain over the past 24 hours with five response choice, including mild, discomforting, distressing, horrible and excruciating.

[Slide]

For the data analysis investigators averaged each patient's daily PPI scores over each week of enrollment in order to calculate weekly average PPI scores. Daily opioid doses were similarly averaged over each week of enrollment to calculate weekly average scores. This information was then used as the basis for determining if patients met the pain progression component of the PFS endpoint. Specifically, pain progression was defined in the study as two consecutive weeks of an increase in weekly average PPI score by one point from baseline or two points from nadir, or an increase in weekly average opioid score by 25 percent or from no opioid use at baseline to any opioid score greater than zero.

[Slide]

With this background in mind, I will now discuss methodologic issues raised by the pain-related endpoints in this application as they pertain to the questionnaire items, study design and reported results.

[Slide]

My discussion of the pain-related measures is based upon support material submitted by the sponsor to the FDA, and no additional dedicated literature review was conducted. Submitted materials relevant to the pain-related endpoint include Melzack's 1975 paper describing the development of the McGill Pain Questionnaire; Graham's 1980 paper which explores use of the McGill Pain Questionnaire in 36 patients with various types of cancer experience in pain; Tannock's 1996 paper reporting results of a clinical trial using the approval of mitoxantrone; Tannock's 2004 paper reporting results of a clinical trial used in the approval of docetaxel; and Berthold's 2006 conference abstract describing a retrospective analysis measuring the ability of

pain reduction to predict survival.

[Slide]

Validity refers to questionnaire's ability to measure what it purports to measure. Both content and construct validity must be established if data collected from a questionnaire is to be considered meaningful.

[Slide]

For a questionnaire to have content validity the wording must have relevance to the study population and it must comprehensively capture the concept of interest, in this case pain intensity. The question must be interpretable by patients and it must be demonstrated empirically that response choice map to meaningful clinical states. It is, therefore, essential to include patient input during early questionnaire development, with subsequent refinement based on patient interviews and dedicated reevaluation of these properties in any population of interest.

However, no patient interviews were documented in the submitted materials to assure

these properties of the PPI. Of particular note, the PPI is purported to assess pain intensity but the third response term, distressing, is not a measure of intensity but, rather, of bother. For example, a patient's pain could be both mild, which is choice number one, as well as distressing. These response choices are, therefore, not mutually exclusive.

[Slide]

For a measure to have construct validity it must be demonstrated that its results favorably compare with results from an independent but similar measure, and that it can discriminate between clinically distinct patient groups in terms of the concept of interest, in this case pain intensity.

However, these properties were not described in submitted materials about the PPI. Although it is useful to demonstrate the ability of a measure to predict a particular clinical outcome such as survival, or to correlate with the radiographic measures such as bone progression, to

have validity it is essential that it be shown to correlate with the concept of interest.

In the Melzack and Graham papers there was poor correlation of PPI scores with multiple other domains of the McGill Pain Questionnaire raising concern about the validity of the PPI if used out of context of the full McGill Pain Questionnaire.

[Slide]

I wish to note that in the submitted mitoxantrone and docetaxel papers content validity and construct validity of the primary pain endpoint model were not explicitly evaluated. These papers describe the results of clinical treatment trials and were not intended as methods papers to validate the PPI. No dedicated patient interviews were conducted to assure comprehension, ordinality of response choices or mapping to concepts of interest. In addition, as I will discuss shortly, the primary pain endpoint model used in ths satraplatin application differs from the primary endpoint model used in the mitoxantrone and docetaxel studies.

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The reliability of a questionnaire is the extent to which responses are free of random error. Most critical in a clinical trial setting is the prospective establishment of reproducibility of responses prior to use of a questionnaire in a study. A measure's ability to detect meaningful changes in clinical status over time should also be determined. These properties of the PPI were not evaluated in the submitted materials.

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Tweaking refers to altering a questionnaire from its original form, a process which requires justification and reevaluation of measurement properties. The PPI as used in this application was altered from the original PPI as described in the Melzack paper. The original PPI asked patients to rate over 24 hours their worst PPI score, whereas this study asked patients to rate over 24 hours their average PPI score. It is unlikely, however, that patients can reliably calculate their average pain over a 24-hour period.

As I mentioned earlier, use of the PPI in the primary PFS endpoint model was altered from the Tannock mitoxantrone and docetaxel primary pain endpoints. For example, in the mitoxantrone study pain relief was the primary endpoint, which was defined as a two-point PPI decrease from baseline or a change from baseline PPI score from 1 to 0 without an increase in analgesic score. Whereas, in this application the primary pain endpoint was pain progression, defined as a one-point PPI increase from baseline or two-point increase from nadir. The opioid endpoints also differed.

Although the mitoxantrone and docetaxel papers both mention a pain progression endpoint in their methods sections similar to that used in this application, no results of such analyses were provided in those papers. Therefore, the measurement properties of a PPI-based pain progression endpoint could not be evaluated based on those prior publications.

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As noted earlier, the investigators

averaged each patient's daily PPI scores over each week of enrollment in order to calculate weekly average PPI scores. But it is not clear that PPI response choices can be averaged. For example, is the average of distressing and excruciating equal to horrible?

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The study was conducted in 16 countries in ten different languages. The PPI and opioid questions were translated in each country by local research assistants without any standardized approach, with no prospective confirmatory patient interviews to assure comprehension or accuracy, and with no back translations to document the validity of the translation process.

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Establishing the clinical relevance of particular score changes is essential for any questionnaire. In the submitted materials, it was not explored what PPI score change is meaningful to patients. For example, the chosen one-point PPI change criterion used in this application means

that a change from no pain to mild pain meets PFS endpoint criteria. But it is not demonstrated by the sponsor that patients would view such a change as meaningful enough to merit use of a cytotoxic agent. Similarly, it is not demonstrated that a 25 percent increase in opioid score alone is meaningful enough to patients to merit toxic therapy.

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This issue becomes relevant when looking at the study results. For example, when analyzing the time to pain progression number of events, a result for which the sponsor provided information about the relative contributions of its two subcomponents, PPI increase and opioid increase, we see zero difference between the satraplatin and placebo groups in terms of the proportions of patients with PPI increases. Hence, the entire between group difference in time to pain progression events overall is driven only by between group differences in opioid use.

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In conclusion, review of this application raises concerns about multiple dimensions of the measurement of its pain-related endpoints. As a result, the validity and reliability of the overarching PFS endpoint model itself, for which the pain progression component is an important driver, also comes into question.

Although I have focused on the pain progression component, similar scrutiny should be given to other components of the PFS composite endpoint. Finally, because of satraplatin's toxicities, including hematologic, gastrointestinal and fatigue manifestations, blinding may not have been maintained, raising questions about the relative contribution of unblinding to observe between group differences.

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Despite my concerns about this application, I want to take a step back and applaud the sponsor for including a pain-related endpoint in this application. This endpoint is clearly very important to patients and providers alike. This

application demonstrates how difficult it is to measure and interpret this type of endpoint.

The FDA guidance on patient-reported outcomes was created precisely because of the types of challenges faced by the sponsor, with the intention to provide greater clarity and to assist investigators who wish to use patient-reported endpoints such as pain intensity in future research. Thank you.

Open Public Hearing

DR. ECKERT: All right. Thank you. We are going to move on to the Open Public Hearing. I will be reading a statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, is drug competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing

to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please only speak when recognized by the chair. Thank you for your cooperation.

MS. CLIFFORD: Our first speaker this afternoon is Joel Nowak.

MR. NOWAK: My name is Joel T. Nowak. I am here today as a consumer and as a representative of the advocacy and educational group Male Care. Neither I nor any member of my family has had any financial interest nor received any support from the applicant. In the interest of fair disclosure, I do wish to add to the record that my primary oncologist is Dr. Daniel Petrylak who is one of the researchers who was involved in the clinical trials.

Unfortunately, I am very familiar with metastatic disease and its effect on patients and the families and society. The 300-family synagogue to which I belong, in the past six years alone, mourned the cancer-related deaths of five men of my

age, all husbands and fathers, productive in their careers and active in the community. In the past two years I have lost my mother to lung cancer, my father-in-law to colon cancer, my sister-in-law to breast cancer and my best friend to kidney cancer.

Although I am only 56 years old, I am a three-time cancer survival. I have been diagnosed and treated for thyroid, prostate and kidney cancer. However, today I am here to discuss my experience with hormone refractory prostate cancer. I was initially diagnosed with prostate cancer in August of 2001 and had a laparoscopic prostatectomy in that October. Then, in December of 2005 I had a recurrence.

As everyone here on the committee knows, recurrent prostate cancer is not a curable disease but it can become a treatable disease if we are allowed to have the drugs that we so desperately need. Those of us who suffer with advanced prostate cancer have already gone through the mill of barbaric treatments. We have had our prostates removed or irradiated, often leaving us with

varying degrees of incontinence and impotence. Despite the primary treatment, 30 percent-B30 percent of us will have a recurrence and develop advanced prostate cancer.

According to the National Cancer Institute, the expected mortality rate for advanced prostate cancer is over 50 percent within 36 months of diagnosis. This signals the beginning of our clock's final countdown, the countdown that will ultimately end in my death, and herein lies my personal predicament. I want ever so much to see my younger son, Max, graduate from college and go to law school. I want to attend my other son's Broadway debut, and I want to dance some day at both of their weddings and to meet my future grandchildren. I don't want my wife, Wendy, to be a widow in her 50s. We have been married for over 33 years and she assures me that she wishes to continue to have a husband to share her life, and I want to be there to hold her and to talk about her dreams about our future.

So, what can I do? As with all men in my

situation, we try desperately to buy even a little bit more time. We try salvage surgery or irradiation. We start a hormone blockade that turns us into physical and chemical eunuchs. We lose the little sexual ability that we mange to cobble together after primary treatment and trade it for hot flushes, loss of muscle mass and bone density, weight gain, peripheral neuropathy, mood swings and a host of other ailments. Despite the suffering that we endure, our cancer continues to march on and our clock continues to unwind.

Now our only option to survive a little longer is chemotherapy. We introduce into our bodies taxotere which will further decimate the already degraded quality of life that we experience. Our goal is simply to push off and delay our inevitable death, to slow down that clock. We want desperately to have more time with our families, more time to be productive citizens and to be loving family members. Satraplatin will not cure my disease but it does offer one more way to make advanced prostate cancer into a treatable

disease. It offers my family and it offers me a way to slow down this too fast ticking clock.

For those of you who are blessedly healthy, the seemingly minimal life extension probably doesn't sound like a lot of time, maybe not even enough time to make it worth your trouble. However, for my family and for me it is not just a few days or a few weeks, it is a whole lifetime. Satraplatin will also delay my progression to pain. I truly believe that, and none of us want to or should have to feel pain.

I still may not live long enough to see my older son successful in the theater or my younger son fulfill his dream of graduating from law school, and I probably will never get to know my grandchildren, but I may have some additional precious time to hold my wife and laugh with my children. Therefore, I wish to urge this committee to recommend to the FDA the approval of the pending application. We need more drugs to be added to our arsenal. Whether they have a minimal or a major effect, we need them.

I appreciate this opportunity to present my position and I thank you for your time.

MS. CLIFFORD: Thank you, Mr. Nowak. I understand our next speaker is Jim Waldenfels.

MR. WALDENFELS: I am Jim Waldenfels and my wife and I will soon be celebrating our 42nd anniversary. We live in Annandale, Virginia. I am on the board of directors of the Virginia Prostate Cancer Coalition. I have attended four national conventions on prostate cancer and I have participated in the AACR's Scientists Survivor Program for two years, and I have been a panel consumer reviewer for the congressionally directed medical research program for two years.

I have no financial ties to the developer of satraplatin and no conflicts of interest. I would first like to thank the FDA for this opportunity to speak in favor of satraplatin, and I would like to thank the ODAC committee members for their service. I am sure I speak for many of us when I say that I appreciate what you do even when you do not do what we, survivors, wish. I

particularly appreciate those who are willing to take controversial stands, and we respect and have high regard for your long records of practice and research on behalf of prostate cancer patients.

Diagnosed in December, 1999, I am a seven and a half year survivor of a challenging case of prostate cancer, featuring an initial PSA of 113, a Gleason of 7 and all biopsy scores positive, most 100 percent. My only therapy has been hormonal blockade, which evolved into triple hormonal blockade intermittently. My first cycle included 31 months on therapy on therapy with a nadir of less than 0.01 and 34 months off therapy, with recovery from all apparent side effects and excellent quality of life after a few months. I am now enjoying my second off therapy period after again achieving a nadir of less than 0.01, and going off therapy after 19 months. At the seven and a half month point, I am again free of all apparent side effects.

I am profoundly grateful for the drugs that have enabled me to do so well, but today I