FDA Briefing Document
Oncology Drugs Advisory Committee Meeting

July 24, 2007

NDA 21801 Orplatna® (satraplatin capsules)

APPLICANT GPC Biotech

Contents

PROPOSED INDICATION 3
EXECUTIVE SUMMARY 3
DRUG DESCRIPTION 6
CLINICAL PHARMACOLOGY 6
Pharmacokinetics 6
Drug Interactions **7**
SPARC STUDY 8
Study Design 8
Treatment 8
Definition of Disease Progression 8
Efficacy Assessments 10
Study Results 11
Statistical Plan 11
Enrollment by Country 11
Prior Chemotherapy 13
PFS Events: Intent-to-Treat Population 13
PFS Overall and By Type of Event 14
Adjudicated Radiologic Studies 14
Time to Pain Progression 15
Best Overall Tumor Response and Response Duration 17
Pain Response and Response Duration 17
Analyses of ITT Population and Subgroup with Prior Docetaxel 18
Drug Exposure 19
Hematologic Toxicity 21
Transfusions 21
Treatment Emergent Non-Hematologic Adverse Events Per Patient With Significantly Higher Incidence in Patients Receiving Satraplatin 22
EORTC STUDY 23
EORTC Study Results 24

PROPOSED INDICATION

"For the treatment of patients with androgen independent (hormone refractory) prostate cancer (HRPC) that has failed prior chemotherapy"

EXECUTIVE SUMMARY

The pivotal study for this NDA is the SPARC study in 950 patients sponsored by the Applicant. A small EORTC study in 50 patients is submitted as a supportive study.

The SPARC study is a multicenter, multinational, double blind placebo-controlled trial with 950 patients with androgen-independent prostate cancer that has failed one (and only one) prior chemotherapy regimen. Patients were randomized 2:1 to Orplatna plus prednisone or placebo plus prednisone. **Placebo patients were not crossed over to Orplatna after progression.** The primary efficacy endpoints are progression-free survival (PFS) and overall survival (OS). Progression events were adjudicated by a blinded independent committee of radiologists and oncologists.

The first issue is the definition of one of the two primary endpoints, PFS. PFS is defined as a composite endpoint, consisting of radiographic progression, symptomatic progression (pain, analgesics, ECOG performance status, weight loss and other clinical events related to prostate cancer) and skeletal related events. The FDA has no prior experience with this endpoint. This was clearly communicated to the Applicant during the development phase. FDA will seek ODAC advice on the acceptability of this composite PFS endpoint as the basis of marketing approval.

Orplatna was better than placebo on the composite PFS endpoint with median PFS 11.1 weeks versus 9.7 weeks (a median difference of 10 days) and HR 0.67 (0.57, 0.77). Orplatna was also better than placebo on PFS defined as only radiologic progression or death with median PFS 36.3 weeks and 20.0 weeks and HR 0.64 (0.51, 0.81). Whether this will translate to OS benefit is unknown at this time.

The second issue is that the two independent radiology readers disagreed on the progression status in 367 of the 950 patients (39%), requiring adjudication by a third independent radiology reader. This raises the question whether PFS could be reliably assessed in this clinical trial.

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 Orplatna toxicities, it is unlikely that blinding was maintained. . In addition, based on a review of background materials provided by the Applicant describing the methods for assessing pain intensity in the SPARC Study, the FDA has determined that the single item Present Pain Intensity Scale

(PPI), derived from the McGill Pain Questionnaire (MPQ), has not been adequately validated for use in this study. The MPQ PPI instrument was used a decade ago in the approval of mitoxantrone for treatment of HRPC, but different criteria for pain response and pain progression were used. Also in the mitoxantrone study the primary endpoint was reduction in pain intensity, while in the Orplatna study the main pain endpoint is time to pain progression. Finally, the FDA Center for Drug Evaluation and Research standards for pain assessment have changed in the interval. In addition, the SPARC protocol did not specify any plan for pain management and pain progression based on increased analgesic use varied widely between countries. Non-narcotic pain medicine usage was not considered in determining pain progression.

The fourth issue is that only 51% of patients had prior docetaxel. Docetaxel is the only drug shown to improve survival in patients with HRPC. All patients should have had prior docetaxel. However, the SPARC trial was started before FDA approval of docetaxel for this use. Subgroup analyses in patients with and without prior docetaxel show that the Orplatna PFS advantage is maintained in both subgroups. Whether there will be a survival advantage in the subgroup with prior docetaxel remains to be seen.

The fifth issue is whether the FDA should wait for the final survival analysis before taking action on the Orplatna application. An interim analysis of overall survival after 463 deaths does not show that Orplatna 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 2007.

The main Orplatna toxicity is hematologic with grade 3-4 neutropenia in 21.1% of patients and grade 4 neutropenia in 4.1% of patients. Infectious episodes occurred in 23.7% of Orplatna patients compared to 11.5% of placebo patients. Grade 3-4 thrombocytopenia occurred in 21.8% of Orplatna patients. Only 2 (0.3%) Orplatna patients had grade 4 thrombocytopenia. Gastrointestinal disorders including nausea, vomiting and diarrhea occurred in 58.5% and 29.1% of Orplatna and placebo patients, respectively. Only 1.9% of Orplatna patients had grade 3-4 diarrhea and 1.6% had grade 3-4 vomiting.

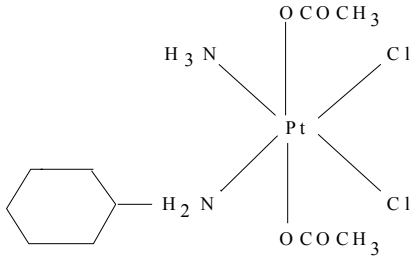
Of note, 14 (2.2%) patients with renal failure were reported in the Orplatna group versus 2 (0.6%) in the placebo group. Serum creatinine elevations were seen in 20.9% (62/313) of the patients in the placebo group and 17.0% (102/629) of the patients in the Orplatna group. A potential interaction between severe hepatic impairment and development of acute renal failure was suggested by a pharmacokinetic study in which 2 of 5 patients with severe hepatic impairment (Child-Pugh Class C) experienced acute renal failure following 1 or more cycles of Orplatna 80 mg/m^2 dx5 q35d. The safety and efficacy of Orplatna in patients with moderate to severe renal impairment, determined by (calculated) creatinine clearance <50 mL/min, have not been established. Biochemical markers for renal function (creatinine and BUN) and hepatic function should be monitored prior to initiating each cycle of treatment and as appropriate.

The EORTC study of similar design to the SPARC study, but in a different patient population (initial chemotherapy in patients with HRPC), was stopped after 50 patients were accrued and provides little support for this NDA.

Recommendation is deferred pending ODAC advice on the above issues.

DRUG DESCRIPTION

Orplatna contains satraplatin, which is an organo-platinum complex described chemically as *(OC-6-43)* bis (acetato) amminedichloro (cyclohexylamine) platinum (IV). The molecular formula is $C_{10}H_{22}$ $Cl_2N_2O_4Pt$ and the molecular weight is 500.3. The structural formula is:



Formulation: Orplatna 10 mg and 50 mg capsules for oral administration.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: After oral administration of a single 80 mg/m^2 Orplatna dose in the fasting state, satraplatin is rapidly absorbed with peak platinum levels occurring 1-4 hours after dosing. Administration of Orplatna after a high fat meal results in a 26% decrease in peak platinum plasma ultra-filtrate concentrations and an 8% decrease in platinum ultra-filtrate AUC.

Distribution: Linear pharmacokinetics are seen at Orplatna oral doses up to 120 mg/m^2. Increase in platinum AUC or peak concentration was not seen with increases in Orplatna oral doses above 200 mg/m^2. After dosing of Orplatna 80 mg/m^2 daily orally for 5 consecutive days the apparent half-life of platinum is approximately 10 days. Orplatna dosing of 80 mg/m^2 once daily for 5 consecutive days results in platinum accumulation ratios of 1.5 and 3 in plasma and plasma ultrafiltrate.

Satraplatin binds irreversibly to serum proteins. Binding of platinum increases as a function of time after oral dosing from 50% at 30 minutes after dosing to approximately 90% at ten hours after dosing.

Metabolism: Satraplatin is extensively metabolized by erythrocytes as well as hepatic enzymes. After 5 consecutive days of Orplatna single oral doses of 80 mg/m^2, no unchanged satraplatin is detected in plasma ultrafiltrate . The only active metabolite identified is a platinum (II) complex that represents 20-30% of the total platinum in plasma ultra-filtrate. The remaining platinum-containing moieties in plasma ultrafiltrate have not been identified. Clinical safety and effectiveness do not show a relationship to platinum ultra-filtrate levels. The major route of platinum elimination in animal studies appears to be renal.

Drug Interactions

Clinical drug interaction studies were not conducted. Satraplatin has been shown *in vitro* to inhibit multiple human cytochrome P450 isoenzymes, including 2D6, 2C9, 3A4 and 1A2. Orplatna may cause an increase in the blood level of drugs that are substrates for cytochrome P450 enzymes.

SPARC STUDY

Study Design

The SPARC study is a multicenter, multinational, double blind placebo-controlled trial with 950 patients with androgen-independent prostate cancer that has failed one (and only one) prior chemotherapy regimen. Patients were randomized 2:1 to Orplatna plus prednisone or placebo plus prednisone. **Placebo patients were not crossed over to Orplatna after progression.** The primary efficacy endpoints are (PFS) and overall survival (OS). Progression events were adjudicated by a blinded independent committee of radiologists and oncologists. Randomization was stratified according to:

• Eastern Cooperative Oncology Group (ECOG) performance status (0-1 *vs.* ≥2);
• Average baseline Present Pain Intensity (PPI) score (0-1 *vs.* 2-5);
• Type of progression on prior chemotherapy (PSA progression only *vs.* tumor progression; patients with both rising PSA and tumor progression were included as tumor progression).

Treatment

For each treatment cycle the dosing schedule was as follows:

Days 1-5:

• Prednisone 5 mg and antiemetic (granisetron or placebo) 1 mg, administered orally 1 hour prior to Orplatna;
• Study medication (Orplatna or placebo) 80 mg/m^2 orally, while fasting (at least 1 hour before a meal or 2 hours after a meal);
• Prednisone 5 mg and antiemetic (granisetron or placebo), administered orally 8 hours after dosing study medication (Orplatna or placebo).

Days 6-35:

• Prednisone 5 mg in AM and 5 mg in PM.

Definition of Disease Progression

Disease progression was defined as a composite endpoint based on the first occurrence of the following:

Radiographic progression, based on RECIST criteria for soft tissue lesions and bone scans for bone lesions. Progression was defined as either a ≥ 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameters recorded since treatment initiation, or unequivocal progression of existing non-target lesions or the appearance of one or more new lesions (or reappearance of any

target lesions that had disappeared), with the following exceptions:

- In cases for which initial tumor flare reaction was possible (e.g., hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms had to persist beyond 4 weeks or additional evidence of progression was required;
- Lesions that appeared to increase in size due to presence of necrotic tissue were not considered to have progressed;
- Intensity changes on bone scans were not used to determine progression, as increased uptake does not constitute unequivocal progression;
- Progression by bone scan alone required two or more lesions; if only one new lesion was documented, the lesion must have been confirmed as being cancerous by additional radiographic studies, starting with a plain radiograph and then followed up with MRI and/or CT scans if the plain radiograph was non-diagnostic; and
- New lesions on bone scan in the presence of improvement of PSA and/or symptoms were not to be considered progressive disease.

Skeletal related events, defined by any observation of the following:

- pathologic bone fracture in the region of cancer involvement;
- radiation therapy to bone;
- cancer related surgery to bone;
- spinal cord or nerve root compression;
- initiation of bisphosphonate therapy in response to new bone pain symptoms; or
- change of antineoplastic therapy for bone pain due to prostate cancer.

Symptomatic progression, defined by observation of any of the following:

- Increase in pain, defined by either an increase in Present Pain Intensity (PPI) score of at least one point from baseline or at least two points compared with the nadir, observed for at least 2 weeks (based on 2 or more consecutive weekly PPI determinations) OR an increase of greater than 25% in weekly average analgesic score maintained for a minimum of 2 consecutive weeks.
  Disease-related pain was followed by a patient diary that recorded pain using the 6-point PPI scale (0=no pain to 5=excruciating pain) of the McGill-Melzack questionnaire and analgesic use on a daily basis, as well as the name, strength, and number of pills or doses used each day. A daily analgesic score was calculated using a numeric scale. A standard dose of narcotic medication was scored as 2 units and higher doses were scored proportionally (e.g., 10 mg morphine = 2 units, 20mg morphine =4 units).
- An increase in ECOG performance status of 2 or more units compared with baseline, attributable to cancer in the investigator's opinion and confirmed by a history exceeding two weeks.
- Weight loss of greater than 10% of initial body weight (taken at last baseline measurement) attributable to cancer in the investigator's opinion; or
- Other clinical events attributable to prostate cancer in the investigator's opinion that required intervention, such as bladder outlet or ureteral obstruction or symptomatic spinal cord compression.

An increase in PSA was not part of this progression endpoint.

Efficacy Assessments

- Bone scans at baseline, after every 2 cycles of treatment for first 6 cycles, then every 3 cycles of treatment until 12 cycles, then every 6 cycles of treatment until disease progression
- CT/MRI scans of abdomen/pelvis and chest x-ray/CT scan at baseline. If positive, repeat every 2 cycles of treatment until disease progression
- Patient daily diaries of pain assessment (PPI score) and analgesic use
- Body weight at baseline and prior to each cycle of treatment;
- Performance status (PS) at baseline and prior to each cycle of treatment

Study Results

Statistical Plan

First Patient Randomized: September 25, 2003
Last Patient Randomized: January 5, 2006
Study Cut-Off Date for Efficacy Analyses: June 15, 2006
Study Cut-off Date for Safety Analyses: November 15, 2006

Initial estimated sample size was 912 patients to have 602 deaths within 36 months (24 months accrual and 12 months follow-up), providing 85% power to detect a 30% increase in median survival from 12 months in the placebo. It was later decided to increase the power to 90%, requiring 700 deaths.

For time to event endpoint (PFS, OS and time to pain progression) analyses the stratified Log Rank Test was used. Hazard ratios were derived using the stratified Cox. The pre-randomization stratification factors were used in both the stratified Log Rank Test and the stratified Cox.

Interim analysis of PFS was done on June 15, 2005 at 354 events and final analysis on June 15, 2006 at 802 events with a prespecified alpha of 0.0244. Final analysis of PFS was specified to be done at about 700 events, but 802 events were included. Interim analysis of survival was done at 463 events and final analysis will be done at 700 events with a prespecified alpha of 0.0444. The 700th survival event is estimated to occur in late 2007.

Enrollment by Country

Country	**Number (%) of Sites**	**Number (%) of Patients**
United States	75 (44.1%)	258 (27.2%)
France	17 (10.0%)	141 (14.8%)
Argentina	15 (8.8%)	98 (10.3%)
United Kingdom	10 (5.9%)	85 (8.9%)
Poland	7 (4.1%)	71 (7.5%)
Germany	12 (7.1%)	61 (6.4%)
Belgium	5 (2.9%)	46 (4.8%)
Spain	7 (4.1%)	42 (4.4%)
Others	22 (12.9%)a	148 (15.6%)b

[a] Others includes Canada (n=1 site), Croatia (n=2), Hungary (n=2), Israel (n=4), Italy (n=4), the Netherlands n=3), Peru (n=3), and Russia (n=3)
[b] Others includes Canada (n=3 patients enrolled), Croatia (n=24), Hungary (n=22), Israel (n=14), Italy (n=23), the Netherlands (n=11), Peru (n=23), and Russia (n=28)

Demographic and Patient Characteristics: ITT Population

Demographic Characteristic	Number (%) of Patients		
	Satraplatin (N=635)	**Placebo (N=315)**	**Total (N=950)**
Age			
N	635	315	950
<65 years	180 (28.3)	93 (29.5)	273 (28.7)
>65 years	455 (71.7)	222 (70.5)	677 (71.3)
>75 years	167 (26.3)	85 (27.0)	252 (26.5)
Median (min-max)	70 (42-88) yr	68 (45-95) yr	70 (42-95) yr
Race			
Caucasian	559 (88.0)	282 (89.5)	841 (88.5)
Black	26 (4.1)	17 (5.4)	43 (4.5)
Latin American	43 (6.8)	13 (4.1)	56 (5.9)
Other d	7 (1.1)	3 (1.0)	10 (1.1)
ECOG Performance Status			
N	635	315	950
ECOG 0-1	570 (89.8)	283 (89.8)	853 (89.8)
ECOG 2	65 (10.2)	32 (10.2)	97 (10.2)
Average PPI Score			
N	635	315	950
PPI 0-1	410 (64.6)	204 (64.8)	614 (64.6)
PPI 2-5	225 (35.4)	111 (35.2)	336 (35.4)
Type of progression after prior chemo			
N	635	315	950
Tumor progression	392 (61.7)	195 (61.9)	587 (61.8)
PSA increase only	243 (38.3)	120 (38.1)	363 (38.2)
Alkaline phosphatase			
N	624	312	936
<1.5 x ULN	374 (58.9)	188 (59.7)	562 (59.2)
>1.5 x ULN	250 (39.4)	124 (39.4)	374 (39.4)
Hemoglobin			
N	633	315	948
>11.0 g/dL	491 (77.3)	253 (80.3)	744 (78.3)
<11.0 g/dL	142 (22.4)	62 (19.7)	204 (21.5)
Lactate dehydrogenase			
N	574	291	865
<2 x ULN	516 (81.3)	260 (82.5)	776 (81.7)
>2 x ULN	58 (9.1)	31 (9.8)	89 (9.4)
PSA			
N	630	313	943
Median (min-max) (ng/ml)	140 (0.1-6084)	134 (0.1-7059)	138 (0.1-7059)
Analgesic score			
N	617	299	916
Median (min-max)	0.0 (0.0-215)	0.0 (0.0-136)	0.0 (0.0-215)

Table continued on following page

Demographic Characteristic	Satraplatin (N=635)	Placebo (N=315)	Total (N=950)
AUA staging at HRPC screening			
N	635	314	949
C2	1 (0.2)	0	1 (0.2)
D2	633 (99.7)	314 (99.7)	947 (99.7)
D3	1 (0.2)	0	1 (0.1)

Prior Chemotherapy*

	Satraplatin	Placebo	Total
Docetaxel	327 (51.5)	160 (50.8)	487 (51.3)
Paclitaxel	17 (2.7)	9 (2.9)	26 (2.7)
Mitoxantrone	128 (20.2)	64 (20.3)	192 (20.2)
Duration of prior chemotherapy			
N	635	315	950
Median (min-max)	20.6 weeks (0.4-381.6)	19.6 weeks (3.0-231.7)	20.4 weeks (0.4-381.6)

* Only prior taxane and mitoxantrone are shown; these do not include all patients, but significant overlap with combination regimens precluded simple treatment categories for other agents

PFS Events: Intent-to-Treat Population

	Number (%) of patients		
	Satraplatin (n=635)	Placebo (n=315)	Total (n=950)
PFS events, n/N (%)	528/635 (83.1%)	274/315 (87.0%)	802/950 (84.4%)
Radiographic progression	189/528 (35.8%)	101/274 (36.9%)	290/802 (36.2%)
Pain	181/528 (34.3%)	117/274 (42.7%)	298/802 (37.2%)
Performance status	15/528 (2.8%)	8/274 (2.9%)	23/802 (2.9%)
Weight	15/528 (2.8%)	7/274 (2.6%)	22/802 (2.7%)
Skeletal related events	22/528 (4.2%)	5/274 (1.8%)	27/802 (3.4%)
Other progressions [a]	58/528 (11.0%)	23/274 (8.4%)	81/802 (10.1%)
Deaths	48/528 (9.1%)	13/274 (4.7%)	61/802 (7.6%)

[a] includes patients receiving a new chemotherapy or steroids considered by the IRC as evidence of progression. In this table, percentages are based on numbers of patients with PFS events.
Modified Applicant Table

PFS Overall and By Type of Event

Analysis	Satraplatin (N=635)	Placebo (N=315)
PFS – ITT Population		
PFS events, n (%)	528 (83.1%)	274 (87.1%)
Mean (SE)	24.9 (1.2) weeks	16.2 (1.2) weeks
Median	11.1 weeks	9.7 weeks
HR (95% CI)	**0.67 (0.57, 0.77) , p <0.001**	
ITT subset with radiologic progression or death*		
PFS events, n (%)	237 (37.3%)	114 (36.2%)
Mean (SE)	45.7 (2.1) weeks	32.3 (2.5) weeks
Median	36.3 weeks	20.0 weeks
HR (95% CI)	**0.64 (0.51, 0.81)**	
ITT subset with pain progression or death*		
PFS events, n (%)	229 (36.1%)	130 (41.3%)
Mean (SE)	53.0 (2.3) weeks	37.6 (2.9) weeks
Median	54.9 weeks	23.9 weeks
HR (95% CI)	**0.64 (0.51, 0.79)**	
ITT subset with other than radiologic and pain progression or death*		
PFS events, n (%)	158 (24.9%)	56 (17.8%)
Mean (SE)	58.0 (2.5) weeks	48.6 (3.5) weeks
Median	66.7 weeks	50.1 weeks
HR (95% CI)	**0.86 (0.63, 1.17)**	

HR: hazard ratio; CI: confidence interval; SD: standard deviation
*** It is to be noted that these include informed censoring. For example, a pain event was censored at the time of event in considering radiologic progression analysis.**
Modified Applicant Table

Adjudicated Radiologic Studies

Type of Progression	Number	Number Adjudicated	Percent Adjudicated
Radiologic Progression	291	136	46.7
Not Radiologic Progression	659	231	35.1
Total	950	**367**	**38.6**

As shown in the above Table, the 2 independent radiologic reviewers disagreed on the progression status of 38.6% (367 of 950) of the patients, requiring adjudication by a third radiologist. This raises the question whether progression could be reliably assessed in this trial.

Time to Pain Progression

Analysis	Satraplatin (N=635)	Placebo (N=315)	p-value
Pain progression events, n (%)	217 (34.2%)	130 (41.3%)	<0.001a
Increase in cancer-related pain	114/217 (52.5%)	57/130 (43.8%)	
>25% increase in opioid analgesic use	103/217 (47.5%)	73/130 (56.2%)	
Mean (SE)	53.0 (2.3) weeks	36.6 (2.7) weeks	
Median	66.1 weeks	22.3 weeks	
HR (95% CI)	**0.64 (0.51, 0.79)**		<0.001b

HR: Hazard ratio, CI: confidence intervals, SE: standard error
[a] log-rank test
[b] Cox Proportional Hazards
Modified Applicant Table

The FDA Center for Drug Evaluation and Research (CDER) Study Endpoints and Labeling Development Team (SEALD) evaluated the methods used for assessing pain in the SPARC Study based on background materials provided by the sponsor. SEALD concluded that an increase in pain, defined by either an increase in Present Pain Intensity (PPI) score of at least one point from baseline or at least two points compared with the nadir, observed for at least 2 weeks (based on 2 or more consecutive weekly PPI determinations) *OR* an increase of greater than 25% in weekly average analgesic score maintained for a minimum of 2 consecutive weeks was an inadequate endpoint in measuring pain progression and should not be included in the composite primary endpoint of PFS. This assessment also applies to the secondary endpoint of time to pain progression.

The use of the PPI in the SPARC Study was justified by the Applicant based upon the precedent established by the pivotal studies supporting the approval of mitoxantrone plus prednisone for palliation of pain in HRPC (Tannock 1996) and docetaxel plus prednisone for the treatment of HRPC (Tannock 2004). However, in both Tannock studies (1996 & 2004), the primary endpoint was "pain palliation," and "pain progression" was a secondary endpoint. In addition, in both Tannock studies (Tannock 1996, Tannock 2004), criteria utilized for "pain progression" were different than the criteria used in the Orplatna SPARC study.

The Present Pain Intensity (PPI) has not been shown to be an adequate or validated measurement of pain progression as defined in the SPARC Study. The single item PPI was obtained from the original parent instrument, the McGill Pain Questionnaire (MPQ). The MPQ was specifically designed for researchers as an interview format and not designed for patient self-reporting. The original MPQ PPI item asked patients to rank their *worst* pain over the past 24 hours, while the PPI used in the SPARC Study asked patients to *average* their pain over 24 hours. The response options for the PPI (1–Mild; 2–Discomforting; 3–Distressing; 4–Horrible; 5–Excruciating) are problematic. There is inadequate evidence that these response options used to describe pain intensity (such as

"distressing") have content validity, can be converted to a numeric equivalent, and that the numbers can be averaged.

There has not been adequate evaluation of the measurement properties of either the PPI or the analgesic use scoring system used in the SPARC Study. Specifically, there has not been evaluation of reliability (test-retest properties, internal consistency, or inter-reviewer reliability), ability to detect change, content validity (i.e., evidence that patients understand terminology or that responses to items actually reflect the intended outcome), or construct validity (i.e., evidence that a measure can discriminate between clinically-defined patient groups). There is insufficient evidence to support the translation and cultural adaptation of the daily diary/pain instrument for use in the multinational SPARC Study.

The interpretation of scores has not been ascertained in order to determine if a 1 or 2 point change in PPI score or 25% change in opioid dose is clinically meaningful. (Is a change in pain score from none to mild or a 25% change of oxycodone dose from 10mg to 12.5mg clinically meaningful)? In considering if a 25% increase in narcotic analgesics is clinically important, if pain palliation is the intent, pain medication might be preferable to Orplatna.

In addition, the SPARC protocol did not specify any plan for pain management and pain progression based on increased analgesic use varied widely between countries. Non-narcotic pain medicine usage was not considered in determining pain progression. Given the toxicity of satraplatin, whether blinding was maintained is questionable.

Interim Overall Survival*

Analysis	Satraplatin (N=635)	Placebo (N=315)	
Death events, n (%)	309 (48.7%)	154 (48.9%)	0.388[a]
Mean (SE)	61.8 (1.7) weeks	58.7 (2.3) weeks	
Median	61.3 weeks	57.3 weeks	
HR (95% CI)	0.90 (0.74, 1.09)		0.296[b]

***Placebo patients were not crossed over to Satraplatin after progression**
HR: Hazard ratio, CI: confidence intervals, SE: standard error
[a] log-rank test
[b] Cox Proportional Hazards model

Best Overall Tumor Response and Response Duration

	Satraplatin N=352[a]	Placebo N=177[a]	P Value
Best Overall Tumor Response (CR+PR)	23/352 6.5%	1/177 0.6%	P=0.001 Fishers Exact
Tumor Response Duration Mean Median	 58.7 weeks 53.3 weeks	 79.3 weeks 79.3 weeks	 N/A

[a] number of patients with soft tissue lesions at baseline

Pain Response and Response Duration

	Satraplatin N=351[a]	Placebo N=181[a]	P Value
Best Overall Pain Response (CR+PR)[b]	85 (24%)	25 (14%)	P=0.005 Fishers Exact
Duration of Pain Response Mean Median	 39.1 weeks 33.6 weeks	 24.1 weeks 19.7 weeks	P= 0.070[c]
HR (95% CI)	0.62 (0.36, 1.07)		P=0.084[d]

[a]Number of patients for whom baseline PPI score and analgesic use were determined with baseline PPI score 1-5, and who had at least 4 consecutive weekly assessments of PPI and analgesic score from the period after treatment initiation until discontinuation of study medication.
[b]Patients with ≥2 point reduction in weekly PPI score from baseline (complete loss of pain if baseline PPI score was <2.0), maintained for ≥5 consecutive weeks, in the setting of a stable or decreasing weekly analgesic score. A stable or decreasing analgesic score was defined as no more than 25% increase from the baseline score.
[c]Log Rank Test
[d]Cox Proportional Hazards model

Analyses of ITT Population and Subgroup with Prior Docetaxel

Analysis	ITT Population		Prior Docetaxel	
	Satraplatin N=635	Placebo N=315	Satraplatin N=327	Placebo N=315
PFS events, n (%)	528 (83.1)	274 (87.0)	273 (83.5)	140 (87.5)
Mean (SE) weeks	24.9 (1.2)	16.2 (1.2)	23.3 (1.6)	14.4 (1.4)
Median (weeks)	11.1	9.7	10.1	9.1
Hazard ratio (95% CI)	0.67 (0.57, 0.77)		0.67 (0.54, 0.83)	
Time to pain progression				
Pain prog. events, n/N (%)	217 (34.2)	130 (41.3)	125 (38.2)	70 (43.8)
Cancer-related pain	114/217 (52.5)	57/130 (43.8)	63/125 (50.4)	26/70 (37.1)
Increase opioid use	103/217 (47.5)	73/130 (56.2)	62/125 (49.6)	44/70 (62.9)
Mean (SE) weeks	53.0 (2.3)	36.6 (2.7)	40.1 (2.0)	33.9 (4.2)
Median (weeks)	66.1	22.3	42.0	21.1
Hazard ratio (95% CI)	0.64 (0.51, 0.79)		0.66 (0.49, 0.89)	
Interim Analysis on Overall survival				
Death events, n (%)	309 (48.7)	154 (48.9)	149 (45.6)	72 (45.0)
Mean (SE) weeks	61.8 (1.7)	58.7 (2.3)	62.3 (2.4)	59.2 (3.4)
Median (weeks)	61.3	57.3	64.0	61.9
Hazard ratio (95% CI)	0.90 (0.74, 1.09)		0.88 (0.67, 1.17)	

CI: confidence intervals, SE: standard error
Modified Applicant Table

Drug Exposure [a]

Satraplatin/Placebo Administration		
Total duration of treatment Median (min-max)	20.4 weeks (4.6 – 170.4)	10.3 weeks (4.7 – 100.6)
Number of treatment cycles per patient, Median (min-max)	4 (1-32)	2 (1-19)
Total cumulative dose (mg) Median (min-max)	2600 mg (260 – 33200)	1700 mg (400 – 19050)
Relative dose intensity (%) Median (min-max)	93.8% (41.5 – 142.5)	96.4% (50.0 – 154.7)
Number (%) patients with Dose reduction (<70 mg/m2) Dose increase (>90 mg/m2) Dose delay ≥7 days	 132 (21.0%) 51 (8.1%) 279 (44.4%)	 1 (0.3%) 32 (10.2%) 33 (10.5%)
Prednisone Administration		
Total duration of treatment Median (min-max)	19.0 weeks (0.1 – 166.0)	10.4 weeks (0.4 – 95.9)
Number of cycles per patient, median (min-max)	4 (1-32)	2 (1-19)
Total cumulative dose (mg) Median (min-max)	1270 mg (5 – 11620)	730 mg (25 – 6710)
Number (%) patients with Dose reduction (<5 mg) Dose increase (≥15 mg) Interrupted cycle	 217 (34.5%) 5 (0.8%) 55 (8.7%)	 100 (31.9%) 1 (0.3%) 12 (3.8%)
Granisetron/Placebo		
Number of cycles per patient Median (min-max)	4 (1-32)	2 (1-19)
Total cumulative dose (mg) Median (min-max)	39 mg (1 – 320)	20 mg (5 - 160)

[a]Doses administered after 15 November 2006 cut-off-date for analysis were not summarized.
max: maximum; min: minimum
Modified Applicant Table

The cut-off date for the safety analyses is November 15, 2006.

The satraplatin group had greater exposure to study drug than the placebo group, based on a median of 4 cycles (range: 1-32) compared to 2 cycles (range: 1-19) of treatment,

respectively. Satraplatin median dose intensity was 93.8% and Placebo 96.4% relative to the planned dose.

Both the satraplatin and placebo groups had equivalent daily doses (10 mg/day) of prednisone. However, the total median exposure to prednisone was 1.7-fold higher for the satraplatin group compared to the placebo group (1270 *vs*. 730 mg), consistent with the median of 4 vs. 2 cycles of treatment for the satraplatin and placebo groups, respectively.

The Applicant tries to make the point that since only the satraplatin group was exposed to active antiemetic and also had double the exposure to prednisone, the safety profile for satraplatin also reflects adverse effects from the antiemetic and prednisone. This is a mute point because the antiemetic is necessary with satraplatin and prednisone is also considered a necessary part of the regimen. The adverse effects seen in this trial are to be expected with general use of the satraplatin regimen.

Treatment-emergent adverse events (TEAEs) resulting in **dose reductions** for study drug were reported for 102 (16.2%) patients in the satraplatin arm and 2 (0.6%) patients in the placebo arm. The majority of dose reductions in the satraplatin arm (78% or 80/102) were due to myelosuppression. TEAEs resulting in **delayed dosing** of study drug (i.e., delays in initiating the subsequent cycle of therapy) were reported for 220 (35.0%) patients in the satraplatin arm and 14 (4.5%) patients in the placebo arm. Overall, myelosuppression was reported as reason for study drug delay in 86.8% (191/220) of the patients who experienced delayed dosing in the satraplatin arm. TEAEs resulting in **discontinuation** of study drug (satraplatin or placebo) were reported for 123 (13.1%) patients, 90 (14.3%) in the satraplatin arm and 33 (10.5%) in the placebo arm.

Hematologic Toxicity

	Number (%) of Patients			Number (%) of Cycles		
Lab Toxicity	**Satraplatin N=629**	**Placebo N=313**	**p-value[a]**	**Satraplatin N=3199**	**Placebo N=1179**	**p-value[a]**
Hemoglobin						
All Grades	605 (96.2%)	282 (90.1%)	<0.001	2827 (88.4%)	824 (69.9%)	<0.001
Grades 2-4	271 (43.1%)	71 (22.7%)	<0.001	716 (22.4%)	110 (9.3%)	<0.001
Grades 3-4	59 (9.4%)	10 (3.2%)	<0.001	91 (2.8%)	13 (1.1%)	<0.001
Grade 4	11 (1.7%)	2 (0.6%)	NS	13 (0.4%)	2 (0.2%)	NS
Platelets						
All Grades	550 (87.4%)	62 (19.8%)	<0.001	2255 (70.5%)	131 (11.1%)	<0.001
Grades 2-4	278 (44.2%)	9 (2.9%)	<0.001	693 (21.7%)	9 (0.8%)	<0.001
Grades 3-4	137 (21.8%)	4 (1.3%)	<0.001	265 (8.3%)	4 (0.3%)	<0.001
Grade 4	2 (0.3%)	0		2 (0.1%)	0	NS
Leukocytes						
All Grades	480 (76.3%)	43 (13.7%)	<0.001	1732 (54.1%)	91 (7.7%)	<0.001
Grades 2-4	302 (48.0%)	7 (2.2%)	<0.001	686 (21.4%)	10 (0.8%)	<0.001
Grades 3-4	86 (13.7%)	2 (0.6%)	<0.001	117 (3.7%)	3 (0.3%)	<0.001
Grade 4	6 (1.0%)	0		6 (0.2%)	0	NS
Neutrophils						
All Grades	420 (66.8%)	15 (4.8%)	<0.001	1224 (38.3%)	23 (2.0%)	<0.001
Grades 2-4	295 (46.9%)	5 (1.6%)	<0.001	608 (19.0%)	8 (0.7%)	<0.001
Grades 3-4	133 (21.1%)	2 (0.6%)	<0.001	190 (5.9%)	3 (0.3%)	<0.001
Grade 4	26 (4.1%)	0	<0.001	28 (0.9%)	0	<0.001

[a]p-values calculated by Fisher's exact test. Caution should be used in interpreting p-values, as the intrapatient laboratory values may not be independent and there is no adjustment for multiple testing.
NS: not significant
Modified Appicant Table

Transfusions

Transfusion	**Number (%) of Patients**		**Number (%) of Cycles**	
	Satraplatin (N=629)	**Placebo (N=313)**	**Satraplatin (N=3199)**	**Placebo (N=1179)**
Red blood cells	102 (16.2)	25 (8.0)	171 (5.3)	32 (2.7)
Platelets	25 (4.0)	1 (0.3)	25 (0.8)	1 (0.1)

Treatment Emergent Non-Hematologic Adverse Events Per Patient With Significantly Higher Incidence in Patients Receiving Satraplatin

	Number of patients-Worst Grade Reported [a]					
	All Grades			Grade 3-4		
Medra System Organ Class & Preferred Term	Satraplatin N=629	Placebo N=313	p-value [b]	Satraplatin N=629	Placebo N=313	p-value [b]
Patients with any TEAE	578 (91.9%)	259 (82.7%)	<0.001	343 (54.5%)	94 (30.0%)	<0.001
Gastrointestinal disorder	368 (58.5%)	91 (29.1%)	<0.001	49 (7.8%)	7 (2.2%)	<0.001
Constipation	144 (22.9%)	34 (10.9%)	<0.001	12 (1.9%)	3 (1.0%)	NS
Diarrhea NOS	156 (24.8%)	19 (6.1%)	<0.001	12 (1.9%)	0	0.011
Nausea	183 (29.1%)	34 (10.9%)	<0.001	8 (1.3%)	1 (0.3%)	NS
Vomiting	104 (16.5%)	28 (8.9%)	<0.001	10 (1.6%)	0	0.036
General disorders & admin. site conditions	276 (43.9%)	107 (34.2%)	0.005	50 (7.9%)	20 (6.4%)	NS
Asthenia	96 (15.3%)	29 (9.3%)	0.011	21 (3.3%)	5 (1.6%)	NS
Fatigue	115 (18.3%)	35 (11.2%)	0.005	11 (1.7%)	4 (1.3%)	NS
Infections & infestations	149 (23.7%)	36 (11.5%)	<0.001	28 (4.5%)	3 (1.0%)	0.003
Influenza	9 (1.4%)	0	0.034	0	0	NS
Upper respiratory tract infection NOS	17 (2.7%)	2 (0.6%)	0.046	0	0	NS
Investigations						
AST increased	15 (2.4%)	1 (0.3%)	0.028	0	0	NS
Metabolism & nutrition disorders	138 (21.9%)	43 (13.7%)	0.003	24 (3.8%)	9 (2.9%)	NS
Anorexia	80 (12.7%)	26 (8.3%)	0.049	4 (0.6%)	2 (0.6%)	NS
Appetite decreased	15 (2.4%)	1 (0.3%)	0.028	0	0	NS
Respiratory, thoracic & mediastinal disorders	123 (19.6%)	34 (10.9%)	<0.001	20 (3.2%)	5 (1.6%)	NS
Cough	38 (6.0%)	7 (2.2%)	0.009	0	0	NS
Dyspnea	45 (7.2%)	11 (3.5%)	0.028	6 (1.0%)	3 (1.0%)	NS
Pulmonary embolism	10 (1.6%)	0	0.036	5 (0.8%)	0	NS
Skin & subcutaneous tissue disorders	89 (14.1%)	32 (10.2%)	NS	6 (1.0%)	0	NS
Alopecia	13 (2.1%)	1 (0.3%)	0.043	0	0	NS
Vascular disorders	74 (11.8%)	20 (6.4%)	0.011	16 (2.5%)	3 (1.0%)	NS
Deep vein thrombosis	10 (1.6%)	0	0.036	4 (0.6%)	0	NS

[a]NCI Common Toxicity Criteria for Adverse Events Version 2.0 [b]p-values calculated by Fisher's exact test. Caution should be used in interpreting p-values, as the intrapatient laboratory values may not be independent and there is no adjustment for multiple testing.
NS: not significantly different. Modified Applicant Table

EORTC STUDY

In this international multi-center, randomized, open-label trial (EORTC study), 50 patients with advanced HRPC who **had not received prior chemotherapy** were randomized to treatment with Orplatna (100 mg/m^2 dx5 days q35d) and prednisone (10 mg bid daily for 35 days) **(n=27)** or prednisone alone 10 mg bid daily for 35 days **(n=23)**. Randomization was stratified for institution, analgesic use (yes *vs*. no), and presence *vs*. absence of clinically evaluable disease. Co-primary endpoints were time to pain progression and overall survival. Secondary endpoints were pain response rate, time to overall progression (TTP), objective response rate and duration of response, PSA response rate, and quality of life assessment. **Confirmed doubling from baseline of PSA to > 20 was a component of the overall progression criteria.**

The treatment groups were balanced for age (median 72.5 years *vs*. 70.4 years for the Orplatna *vs*. prednisone alone groups, respectively), WHO performance status (30% *vs*. 44% WHO 0; 39% *vs*. 37% WHO 1; 30% *vs*. 19% WHO 2), and baseline hematology and serum chemistry parameters.

The study was stopped after accruing only 50 of 380 planned patients because the previous Sponsor terminated their development program. Due to premature termination the study was underpowered. The median progression-free survival was 5.2 vs. 2.5 months for the Orplatna/prednisone and prednisone alone arms, respectively, HR=0.50 (95% CI: 0.28, 0.92).

The difference between treatment groups in overall survival was not significant with median of 14.9 months for Orplatna/prednisone vs. 11.9 months for prednisone alone, HR=0.84 (95%CI: 0.46, 1.55). Because the study was stopped prematurely, assessment of PPI pain scores was stopped and planned endpoints of time-to-pain progression and pain response and pain progression could not be assessed. All the results of this trial are to be interpreted with caution due to very small sample size and very few events.

EORTC Study Results

Analyses	Satraplatin+Prednisone N=27	Prednisone alone N=23
Overall Survival		
Events	23/27 (85.2%)	19/23 (82.6%)
Median (95% CI)	14.9 months (13.7 – 28.4)	11.9 months (8.4 – 23.1)
HR (95% CI)	0.84 (0.46, 1.55)	
Progression-Free Survival[a]		
Events	25/27 (92.6%)	23/23 (100%)
Median (95% CI)	5.2 months (2.8 – 13.7)	2.5 months (2.1 – 4.7)
HR (95% CI)	0.50 (0.28, 0.92)	
Time to Progression[b]		
Events	25/27 (92.6%)	22/23 (95.7%)
Median (95% CI)	5.2 months (2.8 – 13.7)	2.5 months (2.1 – 4.7)
HR (95% CI)	0.53 (0.29, 0.98)	
Biochemical PFS[c]		
Events	25/27 (92.6%)	23/23 (100%)
Median (95% CI)	3.5 months (1.3-8.5)	2.3 months (1.3-2.8)
HR (95% CI)	0.58 (0.32, 104)	

[a]PSA response was included as a component of Progression-Free Survival
[b]Overall progression was defined as the first to occur of (1) ≥1 point increase in PPI score from baseline, confirmed by history exceeding 2 weeks of the requirement for radiation therapy for disease-related pain symptoms; (2) ≥2 point worsening in performance status compared to baseline, confirmed by a history exceeding 2 weeks; (3) progression of measurable or non-measurable disease; and (4) confirmed doubling of PSA to >20 ng/mL, as compared to baseline.
[c] Biochemical PFS defined as time to PSA progression or progression or death
Modified Applicant Table