ORPLATNA®
Satraplatin Capsules

Advisory Committee Briefing Document

NDA 21-801

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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

The proposed indication for Orplatna (satraplatin capsules) is treatment of men with androgen-independent (hormone refractory) prostate cancer (HRPC) that has failed prior chemotherapy. The proposed dosing regimen is 80 mg/m^2, administered once daily for 5 consecutive days, with cycles repeated every 35 days, and continuous treatment with low-dose prednisone (5 mg bid).

Pursuant to agreements negotiated with FDA during End-of-Phase 2 (EOP2) meetings, a Special Protocol Assessment review performed concurrently with the second EOP2 meeting, and a pre-NDA meeting, satraplatin is being considered for accelerated approval based on the protocol-specified early analysis of the SPARC (Satraplatin and Prednisone Against Refractory Cancer) trial, comprising a final analysis of progression-free survival (PFS), with secondary endpoints of time-to-pain progression and interim analysis on overall survival.

The SPARC trial is an international, multicenter, randomized, double-blind, placebo-controlled registrational trial in which 950 patients with advanced HRPC that had progressed after one prior systemic chemotherapy were randomized 2:1 to treatment with satraplatin (80 mg/m^2/day dx5 q35d) plus prednisone (5 mg bid daily) (n=635) or placebo plus prednisone (n=315). All patients in the satraplatin arm received prophylactic 5HT3 antagonist antiemetic whereas dummy placebo antiemetic was given in the placebo arm. Randomization was stratified for performance status (ECOG 0-1 *vs.* 2), average baseline Present Pain Intensity (PPI) score (0-1 *vs*. 2-5), and type of progression after prior chemotherapy (isolated rise in serum levels of prostate specific antigen (PSA) *vs*. tumor progression). For the early analysis for consideration of accelerated approval, the primary endpoint is final analysis of PFS, based on a composite endpoint that did not include PSA progression. PFS was defined as time to disease progression or death, whichever occurred first.

Disease progression in the SPARC trial was defined by a composite endpoint, based on the first occurrence of one of the following: (1) radiographic progression, assessed by bone scans for new bone lesions and x-ray, CT, or MRI for soft tissue lesions; (2) skeletal related events, including pathologic bone fracture, radiation or surgery to bone, spinal cord or nerve root compression, initiation of bisphosphonate therapy for bone pain, or change of anticancer therapy for bone pain; and (3) symptomatic progression, defined by increase in average weekly PPI score or opioid analgesic use, increase in performance status attributable to cancer, weight loss attributable to cancer, or other relevant clinical interventions such as bladder outlet or ureteral obstruction or symptomatic spinal cord compression. The composite endpoint was used to capture all events that are clinically relevant in a highly heterogeneous disease. To avoid ascertainment bias, three independent blinded reviews were performed: (1) all patient pain and analgesic daily diaries were scored independently by two blinded reviewers; (2) all patient radiographic images were reviewed independently by two blinded radiologists; and (3) all pain and analgesic scores, radiology assessments, and clinical events were reviewed independently by two medical oncologists who were blinded to investigator assessments, blood counts, and (except for the first 53 patients) PSA data. As pre-specified in the Statistical Analysis Plan, the progression events and dates assigned by the independent medical oncology review were used for the primary analyses of PFS and time-to-pain progression.

Results from the early analysis of the SPARC trial showed a clinical benefit, including a highly statistically significant 33% reduction in risk of disease progression or death ($p<0.0001$), 36% delay in time-to-pain progression ($p<0.0001$), and approximate doubling of pain and PSA response rates, with a correlation between the two indicating that the effect of satraplatin on pain most likely results from an effect on tumor cells. Importantly, treatment benefits of similar magnitude for both PFS and time-to-pain response were observed regardless of the type of progression event (radiographic or pain); type of prior therapy (docetaxel or other); baseline characteristics such as presence or absence of disease-related pain, performance status, and laboratory parameters; and geographic region (North America, Europe, South America). These findings support the conclusion that satraplatin's utility extends across the highly heterogeneous disease spectrum.

Overall, satraplatin was well tolerated in the elderly patient population (median age: 70 years), which is representative of the overall HRPC population. Myelosuppression was the major toxicity observed with satraplatin therapy, with Grade 3-4 thrombocytopenia in 21.8% of patients and Grade 3-4 neutropenia in 21.1%. However, Grade 4 neutropenia (4.1% of patients), leukopenia (1.0%), anemia (1.7%), and thrombocytopenia (0.2%) were uncommon and febrile neutropenia was rare (0.6%).

The majority of non-hematologic treatment-emergent adverse events (TEAEs) were Grade 1-2 reactions. Among clinically significant non-hematologic events, Grade 3-4 infectious episodes (pooled, 4.5%), diarrhea (1.9% of patients), vomiting (1.6%), and thrombosis (pooled, 1.7%) were also uncommon, but statistically more frequent in the satraplatin arm.

On-study deaths in the SPARC trial (i.e., deaths within 30 days after the last dose of trial drug or resulting from a TEAE) occurred at the same rate in both the satraplatin (4.1% of patients) and placebo (4.5%) arms and were due primarily to disease progression (69% *vs.* 57% of on-study deaths in the satraplatin and placebo arms, respectively).

Overall, considering that it is a chemotherapeutic agent, satraplatin demonstrated a favorable safety profile.

The efficacy and safety findings from the SPARC trial provide evidence *prior to formal demonstration of patient benefit* in this life-threatening disease, as required under Subpart H to make satraplatin available on the market. The patient population is elderly, has a relatively short life-expectancy, and frequently suffers from painful bone metastases. Satraplatin therapy is associated with disease control and pain control. It offers the flexibility of an oral chemotherapeutic option which currently is not available in that setting.

2. BACKGROUND

2.1 Pharmacologic Class and Indication

Satraplatin is an organoplatinum complex that is administered orally. Satraplatin is indicated for the treatment of men with androgen-independent (hormone refractory) prostate cancer (HRPC) that has failed prior chemotherapy. The proposed dosing regimen is 80 mg/m^2, administered once daily for 5 consecutive days, with cycles repeated every 35 days.

2.2 Unmet Clinical Needs for Treatment of HRPC

The patient population presenting with HRPC is typically comprised of elderly men who were diagnosed with prostate cancer in the localized and/or hormone sensitive stage, typically a decade or more prior to the need for chemotherapy. Once hormones are no longer able to control the disease, the patient's condition deteriorates rather rapidly. Docetaxel was approved for first-line chemotherapy of HRPC in 2004 and has become the new standard of care in HRPC; however, this is not a curative treatment so all patients will eventually experience resistance to or toxicity from docetaxel.

Now that systemic chemotherapy is part of the established standard of care for treatment of advanced HRPC, a new unmet medical need has developed. No agent, including docetaxel, has demonstrated a prolongation of progression-free survival (PFS) or overall survival (OS) in this growing group of patients with HRPC whose disease has progressed after first-line therapy. These patients have a short life expectancy, and are often in a poor health condition; for them, disease palliation with minimal toxicity is an important treatment objective.

2.2.1 Treatment of Advanced HRPC Not Previously Exposed to Systemic Chemotherapy

At the time satraplatin development for HRPC was initiated, FDA had approved use of only two agents for palliation of symptoms associated with HRPC. Estramustine was approved in 1981 based on poorly characterized responses observed in a randomized trial *[Edsmyr et al 1978]*. Mitoxantrone plus corticosteroid was approved in 1996 as initial chemotherapy for patients with pain related to HRPC based on results from 2 multicenter, randomized trials that showed a significant treatment effect on pain, without a survival advantage *[Kantoff et al 1999; Tannock et al 1996]*.

In 2004, nine months after the pivotal SPARC trial was initiated, both FDA (in May) and the European Union (in November) approved docetaxel (Taxotere™) in combination with prednisone for the treatment of advanced HRPC, based on results of a large, landmark phase III clinical trial, TAX 327 *[Tannock et al 2004]*. This trial compared docetaxel administered every 3 weeks (q3w) or weekly in combination with prednisone *versus* mitoxantrone in combination with prednisone. For the primary endpoint of survival, docetaxel given every 3 weeks (median survival: 18.9 months) was statistically superior to mitoxantrone plus prednisone (median survival: 16.5 months). In addition, pain reduction and prostate specific antigen (PSA) response rates were significantly higher in the patients receiving docetaxel; however, there was no significant difference in response duration.

Similar significant survival benefits were obtained in a large phase III trial SWOG 9916, that compared q3w docetaxel plus estramustine *versus* mitoxantrone plus prednisone *[Petrylak et al 2004]* in patients with advanced HRPC who had not previously received systemic chemotherapy. In contrast to the TAX 327 trial, the SWOG 9916 trial failed to demonstrate statistically significant differences in pain palliation and quality of life between the two treatment arms *[Southwest Oncology Group 2006]*.

Although docetaxel/prednisone is the only approved therapy for advanced HRPC with impact on survival, the median survival is only 18 to 19 months compared to the control of 16 months and treatment is associated with significant toxicity. In the pivotal TAX327 trial, 30% of patients receiving docetaxel experienced Grade 3-4 neurotoxicity, 42% Grade 3-4 nausea and vomiting, 32% Grade 3-4 neutropenia, and 10% Grade 3-4 cardiovascular toxicity.

2.2.2 Treatment of Advanced HRPC Previously Treated with Systemic Chemotherapy

Patients with HRPC receiving docetaxel eventually have disease progression requiring subsequent treatment. No agent, including docetaxel, has demonstrated a prolongation of PFS or OS for patients with HRPC who have progressed after initial systemic chemotherapy.

Results from small phase II trials of second-line docetaxel treatment for patients with HRPC that had progressed following first-line treatment with mitoxantrone *[Joshua et al 2005; Michels et al 2006; Oh et al 2006; Saad et al 2005]*, first-line docetaxel on different schedules *[Ohlmann et al 2005]*, or first-line experimental agents *[Rosenberg et al 2006]* showed PSA response rates (33% to 72%) similar to those reported for treatment of chemotherapy naïve patients, but PSA response duration was much shorter (about 4 *vs.* 8 months for previously treated compared to chemotherapy naïve patients with advanced HRPC) and tolerability was worse, with about 45% to 65% of previously treated patients requiring a delay, dose reduction, or cessation of docetaxel-based chemotherapy. The median PFS for docetaxel-based chemotherapy in previously treated patients with HRPC, based on PSA response, ranged from 2 to 5 months and median survival was 7 to 13 months.

Small phase II trials of various chemotherapy agents in patients with HRPC that had progressed after initial docetaxel-based chemotherapy, including carboplatin/docetaxel *[Oh et al 2007]*, mitoxantrone *[Michels et al 2006]*, and experimental agents *[Amin et al 2004; Hahn et al 2006; Rosenberg et al 2006]* showed <20% PSA response rate. Based on the available data, there remains an unmet need for chemotherapy that is tolerated and will prolong PFS and/or OS for patients with HRPC that has progressed after (or failed to respond to) first-line docetaxel-based chemotherapy.

2.3 Rationale for Use of Satraplatin in HRPC

2.3.1 Scientific Background

Satraplatin, like other platinum complexes, binds to DNA, producing intra- and inter-strand crosslinks that interfere with DNA replication and lead to cell-cycle arrest and cell death *[Jamieson & Lippard 1999; Mellish et al 1995; Ormerod et al 1996; O'Neill et al 1999; Wang & Lippard 2005]*. However, satraplatin has a number of differences in its chemical structure and physicochemical properties compared with cisplatin, carboplatin or oxaliplatin *[Kelland 2000]* leading to higher lipophilicity and different pharmacokinetic characteristics, including oral bioavailability. *In vitro*, satraplatin and its major biotransformation product JM-118 were found to overcome several of the mechanisms of resistance to cisplatin, including those attributed to platinum transport and alterations in DNA repair processes *[Fokkema et al 2002; Kelland et al 1992a,b; Loh et al 1992; O'Neill et al 1999; Orr et al 1994; Samimi et al 2005; Sharp et al 1994, 1995]*. In particular, results from *in vitro* studies suggest that MMR-deficient cells that are resistant to cisplatin or carboplatin may be sensitive to satraplatin *[Fink et al 1996]*. Additionally, no cross-resistance to satraplatin or JM-118 has been found in cells that are resistant to taxanes, doxorubicin, vincristine, etoposide, mitoxantrone, and camptothecin *[Sharp et al 1998]*.

Satraplatin and JM-118 are active against both androgen-sensitive (LNCaP) and androgen-insensitive (PC-3 and DU-45) prostate cancer cell lines and against taxane-resistant tumor cell lines *in vitro*. The lack of cross-resistance of taxane-resistant cells to satraplatin is of particular importance since docetaxel has become the new standard in the treatment of hormone-refractory prostate cancer patients (first-line chemotherapy). Treatment of LNCaP prostate cancer cells for 42 hours with satraplatin or JM-118 (at IC_{50} concentrations) resulted in a decrease in cell number and a concomitant decrease in secretion of prostate specific antigen (PSA) protein levels, without affecting PSA transcription. Satraplatin, administered orally as 2 cycles of 5 daily treatments with 2 days off-dose between cycles, caused a dose-dependent decrease in growth of PC-3 androgen-insensitive prostate tumors implanted subcutaneously in athymic nude mice.

2.3.2 Clinical Development Program

The early rationale for satraplatin development at Bristol-Myers Squibb (BMS), a previous sponsor, was the observed activity of satraplatin *in vitro* in cells that were resistant to cisplatin and carboplatin. BMS conducted several exploratory clinical trials of satraplatin in highly prevalent cancers, based on promising activity observed for satraplatin in preclinical models and the established clinical use of cisplatin for treatment of several human tumors, including non-small cell and small cell lung cancer, ovarian cancer, and thoracic cancer *[Loehrer & Einhorn 1984; Prestayko et al 1979; Rozencweig et al 1977]*. Although many of the satraplatin trials were terminated early when BMS stopped its satraplatin development program, observed tumor rates for satraplatin were largely consistent with those reported for cisplatin and carboplatin.

Cisplatin, used as single agent, has been evaluated in 6 trials for the treatment of HRPC *[Merrin 1979; Moore et al 1986; Qazi & Khandekar 1983; Rossof et al 1979; Soloway et al 1983; Yagoda et al 1979 a,b]*. The primary endpoint in these trials was response rate in measurable disease. As for other agents in advanced HRPC *[Moore et al 1986; Yagoda et al 1993]*, response rates for cisplatin were discouraging, with half the trials concluding that cisplatin was

not active at the dose and schedule studied *[Qazi & Khandekar 1983; Soloway et al 1983; Yagoda et al 1979a,b]*.

Because satraplatin had shown activity in some platinum resistant tumor models *in vitro*, BMS performed two pilot, open-label trials to assess the efficacy and safety of satraplatin for treatment of advanced HRPC in both chemotherapy naïve and previously treated patients. In the first trial *[CA142-013]*, satraplatin (120 mg/m^2 dx5 q28d) was administered to 39 patients with advanced HRPC who had not previously received chemotherapy; PSA responses were observed in 31% (10/32 evaluable; 2CR, 8PR) of patients and objective tumor responses were observed in 8% (1/12; 1PR) of patients with measurable disease who received at least 2 courses of treatment. In the second trial *[CA142-026]*, satraplatin (80 mg/m^2 dx5 q35d) was administered to only 10 patients with HRPC that had failed mitoxantrone/corticosteroid treatment and had worsening pain before BMS terminated its satraplatin development program; PSA responses were observed in 22% (2/9 evaluable; 2PR) of patients.

Based on findings from these pilot trials, BMS initiated two phase III trials in HRPC. The first phase III trial *[CA142-025, EORTC 30972; Sternberg et al 2005]* was a randomized open-label trial through the European Organization for Research and Treatment of Cancer (EORTC) to evaluate the efficacy and safety of satraplatin (100 mg/m^2 dx5 q35d) plus prednisone (10 mg bid dx35) *versus* prednisone alone in patients with HRPC who had not received previous chemotherapy. The trial was stopped after enrolling only 50 of the planned 380 patients because BMS terminated its satraplatin development program, but, subsequently, results showed a significant increase in PFS (5.2 *vs*. 2.5 months, p=0.023; HR=0.50, 95% CI: 0.28-0.92) and PSA response rate (33% *vs*. 9%) and a trend toward longer survival with satraplatin (14.9 *vs.* 11.9 months; HR=0.84, 95% CI: 0.46-1.55), suggesting a significant treatment benefit with satraplatin for patients with advanced HRPC not previously exposed to systemic chemotherapy.

The second phase III trial *[CA142-029]* was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of satraplatin (100 mg/m^2 dx5 q35d) plus prednisone (10 mg bid dx35) in patients with advanced HRPC who had disease-related pain. BMS discussed this trial design with FDA and received FDA's agreement to proceed with this as a registrational trial. Both treatment-naïve and patients who had received one prior chemotherapeutic regimen were eligible for this trial. This trial was stopped after enrolling only 14 of the planned 360 patients because BMS terminated its satraplatin development program. Although most planned efficacy assessments were not performed because of the early termination, at the end of trial investigators reported 57% (4/7; 4PR) PSA responses with satraplatin plus prednisone compared to 29% (2/7; 1CR, 1PR) with placebo plus prednisone.

GPC Biotech considered that the results obtained in clinical trials of satraplatin in HRPC, particularly results from the EORTC trial, were sufficiently promising to justify initiation of the pivotal SPARC trial *[GPC SAT3-03-01]*. The decision by GPC Biotech in 2003 to initiate a pivotal trial in previously treated patients with advanced HRPC was based on consideration of an evolving standard of care for chemotherapy-naïve patients, with pivotal trials of docetaxel-based regimens for treatment of chemotherapy-naïve patients with advanced HRPC nearing completion.

3. OVERVIEW OF BIOPHARMACEUTICS

Satraplatin is a low solubility (~0.4 mg/ml at pH 1-7.5), low permeability (P_{app} much less than pindolol) substance, *i.e.,* Biopharmaceutics Classification System (BCS) Class 4. Satraplatin particle size (*i.e*., microcrystalline particles of 0.3-1.8 μm compared to the standard crystalline material with a particle size of 10-200 μm) did not appear to affect the results observed in *in vivo* efficacy studies; therefore, particle size reduction to increase absorption and/or efficacy was not pursued.

All clinical trials have used an oral formulation comprised of a dry blend of satraplatin and commonly used excipients of USP/NF quality (anhydrous lactose; microcrystalline cellulose (Avicel PH102), sodium starch glycolate, and magnesium stearate) filled into hard gelatin capsules.

The proposed commercial formulations consist of a 10 mg and a 50 mg capsule. The formulations used in all GPC Biotech sponsored studies, including the pivotal phase III SPARC trial, are identical to the proposed commercial formulation.

The excipients utilized by BMS and GPC Biotech were identical. Although there were differences in the ratio of excipients in the BMS and GPC Biotech capsules, there were no apparent differences in dissolution profiles between the two capsule formulations; therefore, it is unlikely that a bioavailability difference between the BMS and GPC Biotech formulations would be observed.

The absorption of satraplatin is affected by administration of the drug with food. There was a 26% reduction in platinum C_{max} and approximately an 8% reduction in platinum AUC when satraplatin was administered with a standard high fat meal *[SAT1-04-01]*. The lower limit of the 90% confidence intervals for both C_{max} and AUC were below the 80% acceptance criteria (56.14% and 73.53%, respectively). The clinical significance of the decrease in absorption is not known, therefore, it is recommended that satraplatin be administered to patients in a fasted state, i.e., 1 hour before or 2 hours after a meal.

4. OVERVIEW OF CLINICAL PHARMACOLOGY

4.1 Clinical Pharmacokinetics of Satraplatin in Cancer Patients

Satraplatin pharmacokinetics (PK) were evaluated by assessing platinum concentrations in plasma and plasma ultrafiltrate (PUF) as a primary measure of exposure, consistent with evaluations performed for other marketed platinum complexes, including cisplatin, carboplatin, and oxaliplatin.

4.1.1 Absorption

To characterize the pharmacokinetics, safety and tolerance of satraplatin at doses between 60 and 700 mg/m^2, an ascending, single oral dose trial was conducted in cancer patients *[CA142-001; McKeague et al 1995]*. To assess if higher exposures could be obtained and tolerability improved when the satraplatin dose was fractionated into twice daily instead of once daily dosing, satraplatin was given in a divided-dose trial as two oral doses, approximately 12 hours apart *[CA142-011; Beale et al 1998]*. Following the completion of the above trials, three separate ascending, multiple dose trials were conducted evaluating the pharmacokinetics, safety and tolerance of oral satraplatin administered for 5 consecutive days at doses between 30 and 140 mg/m^2 *[CA142-002; CA142-003/009; CA142-012; Kurata et al 2000; McKeague et al 1997]*. A GPC Biotech-sponsored trial *[SAT1-04-01]* was performed to characterize the pharmacokinetics of satraplatin at the dose utilized in the pivotal SPARC trial (80 mg/m^2/day for 5 consecutive days, repeated every 35 days).

Results from these clinical trials showed that satraplatin is rapidly absorbed after oral dosing, with peak concentrations of platinum in plasma and PUF occurring typically within 2 hours after administration *[SAT1-04-01]*. The absolute bioavailability of satraplatin in man is not known due to the lack of availability of an intravenous dosage form. Results from a food-effect trial showed that administration of satraplatin after a high fat meal significantly decreased the rate and extent of absorption of platinum *[SAT1-04-01]*. Because the clinical significance of these changes is not known, it is recommended that satraplatin be administered either 2 hours after or 1 hour before a meal.

Satraplatin exposure (*i.e.,* area under the plasma or PUF platinum concentration curve [AUC]) increased as the dose was increased up to 120 mg/m^2. There was not a dose-proportional increase in exposure for doses from 120 mg/m^2 up to 700 mg/m^2 *[CA142-001; McKeague et al 1995]*, likely attributable to solubility-limited absorption. Therefore, administration of satraplatin at doses above 120 mg/m^2 does not appear to be justified.

4.1.2 Distribution

The protein binding of satraplatin was characterized *in vitro* using human serum. In addition, *ex vivo* evaluations of satraplatin protein binding were conducted by comparing concentrations of platinum in plasma ultrafiltrate (PUF) and in plasma samples collected from patients having received oral satraplatin. Results showed that the protein binding of platinum in man after administration of satraplatin is irreversible and the extent of binding increases as a function of time after dosing. There was no relationship between total platinum concentration in plasma and the extent of binding of platinum to plasma proteins. Irreversible binding of platinum as well as

time-dependent binding of cisplatin to plasma proteins also have been observed with oxaliplatin and carboplatin *[Ma et al 1996; Gaver et al 1987; Graham et al 2000]*.

4.1.3 Metabolism

To gain insight into the mechanism of satraplatin metabolism, *in vitro* metabolic stability studies were performed using whole blood, cytochrome P450 (CYP450), supersomes and microsomes. Based on *in vitro* data, satraplatin is metabolized by erythrocytes as well as liver microsomal enzymes. The ubiquitous nature of erythrocytes suggests that satraplatin metabolism will not be affected either by other drugs or by alterations in hepatic function.

Satraplatin is rapidly metabolized to JM-118 and other platinum containing moieties after oral administration. Metabolic "fingerprints" after oral administration of satraplatin to rat, dog and man have been generated using LC-ICP/MS. Peaks corresponding to the retention times of platinum-containing peaks in man were present in both the rat and dog. This implies that the metabolic profile of satraplatin is similar in the three species and justifies the use of the rat and dog as toxicology models. JM-118 accounted for approximately 20% - 30% of the platinum content in PUF; the remaining platinum containing moieties have not yet been elucidated. Studies are ongoing to identify the remaining platinum-containing moieties in PUF; however, elucidation and identification of satraplatin metabolites is technically difficult due to the lack of suitable techniques for the separation and detection of platinum containing moieties.

4.1.4 Excretion

The half life of platinum in plasma and PUF after oral administration of satraplatin is approximately 230 hours in patients with normal renal and hepatic function *[SAT1-04-01; SAT1-04-03; SAT1-04-04]*. As a result, platinum accumulates in plasma and PUF after repeated administration of satraplatin with accumulation factors of 3 and 1.5 in plasma and PUF, respectively, after 5 days of daily dosing. The accumulation at steady state has not been determined because steady state would require at least 4 to 5 half lives of repeated dosing (*i.e.* at least a month of continued dosing).

The pharmacokinetics of platinum following oral administration of satraplatin to cancer patients with renal impairment *[SAT1-04-03; Hong et al 2006]* and hepatic impairment *[SAT1-04-04; Setlik et al 2006]* is the subject of ongoing clinical trials. The interpretation of the effect of these intrinsic factors on satraplatin disposition are complicated because conclusions will be based on measurement of total platinum in plasma ultrafiltrate (i.e., free platinum) rather than measurement of individual active platinum containing moieties.

Preliminary findings suggest that renal elimination represents the primary route of elimination of platinum after oral administration of satraplatin and that hepatic impairment may not significantly alter the pharmacokinetics of platinum after oral administration of satraplatin. It is premature to formulate specific recommendations for modifying dosage regimen in patients with either renal or hepatic impairment because these trials have not yet been completed. Patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min) were enrolled in SPARC; these patients appeared to have slightly higher rates of myelosuppression after all cycles, but there was no correlation between baseline creatinine clearance and hematologic events. A reduction in the prescribed satraplatin dose may be necessary in patients with (calculated) creatinine clearance values <30 mL/min.

4.2 Drug-Drug Interactions

Satraplatin is a non-specific inhibitor of multiple CYP450s (*i.e.*, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) *in vitro*. In contrast, JM-118, the predominant metabolite of satraplatin, is not an inhibitor of CYP450 isozymes. Since satraplatin concentrations are undetectable (*i.e.,* below the limit of quantitation of 5 ng/mL) after oral administration and the primary satraplatin metabolite is not an inhibitor of CYP450s *in vitro*, there is a high probability that the oral administration of satraplatin will not cause clinically significant drug-drug interactions. However, the clinical implications of the *in vitro* data have not been determined in a clinical drug interaction trial to date. No significant difference in the frequency of adverse experiences was observed in the SPARC trial with or without concomitant medication with a significant dependency on CYP metabolism for elimination.

In vitro, satraplatin does not induce CYP450s nor does it inhibit Pgp. Therefore, it is unlikely that satraplatin will affect the disposition of other drugs through these mechanisms.

4.3 Satraplatin Pharmacodynamics

Several clinical trials sponsored by BMS have reported a relationship between platinum exposure (*i.e.,* AUC) in PUF and thrombocytopenia after repeated oral administration of satraplatin for up to 5 days *[CA142-001; CA142-002; CA142-012; McKeague et al 1995, 1997; Kurata et al 2000]*. A relationship between platinum PUF exposure and neutropenia and leukopenia was observed in a phase I trial in Japan *[CA142-012; Kurata et al 2000]*.

The maximum tolerated dose (MTD) of satraplatin decreased with duration of dosing. The MTD decreased from above 700 mg/m^2 after a single dose (it was not possible to determine an MTD because of absorption becoming saturated at higher doses) *[CA142-001; McKeague et al 1995]* to 140 mg/m^2/day after 5 days of dosing *[CA142-002; CA142-012; McKeague et al 1997; Kurata et al 2000]* and to 45-50 mg/m^2/day after 14 days of dosing *[CA142-007; Sessa et al 1998]*.

5. SPARC TRIAL OBJECTIVES AND DESIGN

The primary objectives of the SPARC (Satraplatin and Prednisone Against Refractory Cancer) trial *[GPC SAT3-03-01]* were to compare PFS and OS in patients with stage D2 HRPC randomized to either satraplatin plus prednisone or placebo plus prednisone after failure of first-line chemotherapy for metastatic disease. Other objectives of the trial were to compare the time-to-pain progression (secondary endpoint), pain response, tumor response and PSA response (exploratory endpoints) as well as assess the safety of satraplatin in this setting.

The SPARC trial is a multinational, multicenter, randomized, double-blind, placebo-controlled phase III trial. Key design features, summarized below, were discussed with FDA during End-of-Phase 2 (EOP2) meetings on 01 October 2002 and 02 July 2003, and in a Special Protocol Assessment (SPA) review performed concurrent with the second EOP2 meeting. At these meetings, FDA agreed to consider early analysis of the SPARC trial for consideration of accelerated approval based on the protocol-specified final analysis of PFS, with secondary endpoints of time-to-pain progression and interim analysis on OS. The final trial analysis will use OS as the primary endpoint and is projected to be available in late 2007.

5.1 Choice of Patient Population

Advanced HRPC is a heterogeneous disease *[Shah et al 2004]*. After intensive discussions with leading oncologists and urologists on this topic, the SPARC trial was designed deliberately to have broad eligibility criteria that would enable the evaluation of satraplatin in a representative range of patients with HRPC. Thus, patients with either disease progression or PSA progression after cytotoxic chemotherapy for metastatic disease were to be included, as well as patients with symptomatic or asymptomatic disease, and patients with measurable or nonmeasurable disease.

Patients were required to have metastatic disease, a minimum life expectancy > 3 months and a performance status ECOG ≤2. They must have recovered from all side effects of prior treatment, and adequate function of the bone marrow, liver and kidney was required. Patients with stabilized bisphosphonate and analgesic therapy were permitted to continue these treatments.

Prior cytotoxic chemotherapy included docetaxel and mitoxantrone, as well as estramustine if used in the hormone refractory setting. Patients with more than one prior cytotoxic chemotherapy regimen were excluded.

Prior Docetaxel Treatment: At the time the SPARC trial was initiated, docetaxel had not been approved by FDA (or EMEA) for treatment of HRPC, though pivotal studies in patients with HRPC who had not previously received cytotoxic chemotherapy for metastatic disease were nearing completion. The SPARC trial was designed to include patients who had failed initial docetaxel-based chemotherapy, as well as those not previously exposed to docetaxel.

During the pre-NDA meeting held on 21 June 2005, FDA reviewers expressed concern that prior docetaxel treatment may affect survival of patients with advanced HRPC receiving subsequent chemotherapy because of the survival advantage demonstrated for docetaxel-based chemotherapy at initial treatment. However, the limited evidence currently available refutes this concern: PFS data, which have been reported publicly for only one of the docetaxel phase III trials in chemotherapy naïve patients with advanced HRPC, showed equivalent overall survival

after disease progression for both the docetaxel/estramustine and mitoxantrone/prednisone groups (12 *vs.* 13 months, respectively) *[Petrylak et al 2004]*.

As an additional consideration, since satraplatin has a unique and non-cross resistant mechanism of action compared with the classes of agents used for initial chemotherapy for advanced HRPC, including taxanes (docetaxel, paclitaxel) and mitoxantrone, it is unlikely that the type of prior chemotherapy will affect potential responses to satraplatin. In particular, preclinical studies showed that satraplatin is effective in docetaxel-resistant cancer cell lines *[Sharp et al 1998]*.

Symptomatic versus Asymptomatic Disease: Although FDA initially recommended that two pivotal studies be performed, one in asymptomatic patients and the other in patients with disease-related pain, in view of the evolving standard of care for HRPC, GPC Biotech concluded that a large trial in a population of asymptomatic patients was not feasible. During End-of-Phase 2 (EOP2) meetings and discussions of Special Protocol Assessment review issues in July 2003, FDA reviewers agreed that a primary analysis based on the total trial population and a secondary subset analysis comparing patients who were asymptomatic *versus* symptomatic at trial entry would be acceptable.

Geographic regions: In order to expedite accrual, patients for the SPARC trial were recruited from North America, Western and Eastern Europe, South America, and the Middle East (Israel). Although consistent findings in pharmacokinetic studies conducted in Europe, Japan, and the U.S. suggested that satraplatin efficacy would not be dependent on ethnic or intrinsic factors, subgroup analyses were performed to explore the possible effects of extrinsic factors.

Baseline prognostic factors: Advanced HRPC is a heterogeneous disease *[Shah et al 2004]*, and treatment results are correlated with baseline prognostic factors including performance status, hemoglobin, alkaline phosphatase, lactate dehydrogenase (LDH), and bone pain *[Fossa et al 1992; Halabi et al 2003; Petrylak et al 1992; Smaletz et al 2002]*. The SPARC protocol included stratification for the following prognostic factors:

- Performance status (ECOG 0-1 *versus* 2);
- Average baseline Present Pain Intensity (PPI) score (0-1 *versus* 2-5); and
- Type of progression after prior chemotherapy (isolated PSA rise *versus* tumor progression; patients with both tumor progression and PSA progression were stratified as tumor progression).

Additionally, the following factors were examined at the time of analysis to assess the extent to which there were imbalances between treatment arms:

- Hemoglobin level (≥11 g/dL *versus* <11 g/dL);
- Alkaline phosphatase (<1.5 x ULN *versus* ≥ 1.5 x ULN);
- LDH (<2 x ULN *versus* ≥2 x ULN).

5.2 Choice of Control

Patients who had failed taxane-based regimens were eligible for the SPARC trial. Since there is no approved second-line therapy for these terminal patients, a placebo control arm was considered ethical and appropriate by medical oncologists in both the U.S. and Europe. Corticosteroid generally is not discontinued in the palliative setting despite progressive

malignancy. Accordingly, both the satraplatin and placebo arms included prednisone at a relatively low dose (5 mg bid) that was not expected to contribute to anticancer efficacy.

5.3 Dose Selection

Phase I dose-finding and pharmacokinetic trials conducted in Europe *[CA142-002; McKeague et al 1997]* and Japan *[CA142-012; Kurata et al 2000]* recommended daily doses of 100 mg/m^2 and 120 mg/m^2 for previously treated and untreated patients, respectively, administered for 5 consecutive days, with cycles repeated every 4 to 6 weeks. However, experiences from previous studies of satraplatin in HRPC suggested that the recommended doses from Phase I studies may not be tolerated in this indication:

- A pilot trial of satraplatin conducted in patients with advanced HRPC who had not previously received cytotoxic chemotherapy *[CA142-013]* specified a starting regimen of 120 mg/m^2 dx5 q21d, but lengthened cycles to 28 days to accommodate late hematologic nadirs (mean neutrophil and platelet nadirs at 26 and 24 days, respectively).
- The EORTC trial *[CA142-025]* found that a regimen of 100 mg/m^2 dx5 q35d was well tolerated in patients with advanced HRPC who had not previously received cytotoxic chemotherapy, but the relative dose intensity in patients with prolonged exposure to satraplatin was closer to 80 mg/m^2.
- A pilot trial of satraplatin conducted in patients with advanced HRPC previously treated with chemotherapy *[CA142-026]* specified a starting dose of 100 mg/m^2 dx5 q35d, but the protocol was amended to a dose of 80 mg/m^2 because 2 of the first 4 patients experienced febrile neutropenia and severe thrombocytopenia.

Based on these experiences, a regimen of 80 mg/m^2 dx5 q35d was selected for the SPARC trial in previously treated patients with advanced HRPC. There were provisions for up to 2 dose reductions (from 80 mg/m^2 to 60 mg/m^2 to 40 mg/m^2) for toxicity and delayed recovery; patients who had a dose reduction were not eligible for re-escalation. A single dose escalation (from 80 mg/m^2 to 100 mg/m^2) was allowed for patients who completed at least 2 cycles of therapy and had no $\geq$ grade 2 hematologic toxicities, no $\geq$ grade 2 gastrointestinal toxicities (while receiving loperamide treatment), no grade 4 fever toxicities, and no dosing interruption or delay ($\geq$ 6 weeks) due to toxicities.

5.4 Trial Endpoints for Early Submission for Accelerated Approval

The SPARC trial has two primary efficacy variables: progression-free survival (PFS), with progression events adjudicated in a blinded fashion by an Independent Review Committee (IRC), and overall survival (OS). For the early analysis for consideration of accelerated approval, the primary endpoint is the final analysis of PFS and secondary endpoints are time-to-pain progression and interim analysis on OS. The final analysis for full approval will utilize OS as the primary endpoint; this analysis has not yet been performed because the required number of deaths (700) has not yet been observed.

As pre-specified in the Statistical Analysis Plan (SAP), PFS is defined as the time from randomization to the first IRC documented progression or death due to any cause. In the absence of a PFS event before the 15 June 2006 cutoff date, PFS was censored at the last assessment date prior to discontinuation and before the cutoff date. Patients who left the trial without an IRC

documented progression and died before the 15 June 2006 cut-off date had their death assigned as a PFS event; these patients were not censored if and when subsequent anticancer therapy was given prior to death. Patients who left the trial without an IRC documented progression and did not die prior to the 15 June 2006 cutoff were censored for progression at the date of their last assessment for disease progression. PFS of a patient with no on-study assessment was censored at the randomization date.

Overall survival (OS) is defined as the time from randomization to death due to any cause. Living patients were censored on the last date the patients were known to be alive. OS of any patient, with a date of death or date of last contact after the cut-off date of 15 June 2006, was censored at 15 June 2006.

In the protocol reviewed by FDA in July 2003 in the Special Protocol Assessment, the protocol-specified primary endpoint was time to progression (TTP). In April 2005, FDA issued a Draft Guidance entitled "*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics"* that provided FDA's current thinking on the use of TTP *versus* PFS as endpoints in cancer trials. In summing up the comparison the Guidance states that *"Therefore, in most settings PFS is the preferred regulatory endpoint."* Indeed, for the particular patient setting, an endpoint based on disease progression may have advantages compared to survival including earlier occurrence and higher disease specificity. During the pre-NDA meeting in June 2005, FDA reviewers agreed with GPC Biotech's proposal to make PFS the primary endpoint for both FDA and EMEA filings.

In the U.S., the FDA approach to a regular approval based on a PFS endpoint was discussed on various occasions. In the EOP2 meeting held on 02 July 2003, FDA indicated that interim and final analyses "*can be based on TTP if TTP is appropriately defined. The requirements for a surrogate supporting regular approval are more demanding that those for a surrogate supporting accelerated approval*". In the pre-NDA meeting held on 21 June 2005, FDA reviewers indicated that "*accelerated approval based on an interim analysis of TTP will be considered*", but noted that "*the size of the progression free survival effect and the fact that one-half of the patients have not had Taxotere which may improve their survival will be considerations in the evaluation of PFS as an endpoint for accelerated approval*".

Following the pre-NDA meeting at the FDA and prior to unblinding trial results, the Statistical Analysis Plan was revised to implement the recommendations GPC Biotech had received from the agencies. The two major revisions were: (1) replacement of TTP with PFS as a primary endpoint for consideration of accelerated approval at the time of final PFS analysis and (2) specification of overall survival (OS) as the other primary endpoint.

5.5 Definition of Disease Progression

Per protocol, disease progression was defined as a composite endpoint based on the first occurrence of one of the following:

- Radiographic progression, based on RECIST Criteria for soft tissue lesions assessed by abdominal scans and chest x-rays/scans *[Therasse et al 2000]* and bone lesions assessed by bone scans. Progression by bone scan alone required 2 or more new lesions; if only a single 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;

- 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 $\geq$1 point from baseline or $\geq$2 points from nadir, observed for at least 2 weeks (based on 2 or more consecutive weekly PPI determinations) *OR* an increase $\geq$ 25% in weekly average opioid analgesic score maintained for a minimum of 2 consecutive weeks;
  - Increase in ECOG performance status of $\geq$2 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.
- Death from any cause.

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

5.5.1 Pain Scoring and Validation; Central Review and Scoring of Pain and Analgesic Diaries

Regulatory Precedent for Pain Scoring: Prostate cancer metastasizes most often to pelvic lymph nodes and to bone, with pain and fatigue as major symptoms. Patients with pain due to metastases to bone generally require regular narcotic medication, titrated to provide maximum relief from pain. Given that pain is a common and disabling symptom of HRPC, assessment of pain, together with a measure of analgesic intake, has been considered an appropriate and validated method for evaluation of symptom control in clinical trials directed toward patients with HRPC.

FDA approval of mitoxantrone plus prednisone for palliative treatment of symptomatic HRPC was based on a randomized phase III trial with a primary endpoint of pain relief, assessed using the same instruments and scoring system used in the SPARC trial, i.e., PPI score and analgesic consumption *[Tannock et al 1996]*. This regulatory precedent established the validity of using PPI and analgesic consumption as a measure of pain (and change in pain) in patients with HRPC.

More recently, a retrospective analysis of the pivotal TAX 327 trial, which was the basis for FDA approval of docetaxel plus prednisone for treatment of HRPC, showed that pain response in men with symptomatic HRPC, assessed using PPI score and analgesic consumption, is an independent predictor of survival *[Berthold et al 2006]*. This finding further establishes the

validity and clinical meaningfulness of pain assessments using PPI score and analgesic consumption in patients with HRPC.

While the pivotal mitoxantrone and docetaxel trials and SPARC trials all used the same assessment tools—PPI score and analgesic score—there were several important differences between the pain assessments in the previous pivotal trials and those in the SPARC trial:

- Duration of change in scores for pain response
  Pain response in the pivotal mitoxantrone trial was determined by comparing 2 PPI and analgesic scores performed 3 weeks apart, whereas the pivotal SPARC trial compared weekly average PPI and analgesic scores for 5 consecutive weeks, comprising at least 15 individual assessments. The use of a larger number of assessments and the requirement that an improvement in scores be observed for at least 5 consecutive weeks (rather than 3 weeks) is a far more demanding requirement for pain response.
- Duration of change in scores for pain progression
  Pain progression in the SPARC trial was based on worsening of weekly average PPI or opioid analgesic scores for at least 2 consecutive weeks, comprised of at least 6 individual assessments, whereas the pivotal mitoxantrone trial involved only 2 assessments performed 3 weeks apart.
- Blinded *versus* unblinded assessments
  In the pivotal mitoxantrone and docetaxel trials, scoring and assessment of pain response and pain progression was performed by individual investigators. In contrast, for the SPARC trial scoring of patient diaries and calculation of weekly average PPI and analgesic scores was performed centrally by blinded reviewers. These data were then provided to an Independent Review Committee (IRC), comprised of 2 blinded medical oncologists, who determined pain response and pain progression according to pre-specified criteria. The use of blinded scorers and assessors avoided the potential for investigator assessment bias.
- Types of analgesics evaluated
  The pivotal mitoxantrone and docetaxel trials considered both narcotic and non-narcotic analgesics in deriving the analgesic score. In contrast, the SPARC trial considered only narcotic analgesics in deriving the analgesic score because prostate cancer and pain experts advised that progressions due to increased use of narcotic analgesics were clinically relevant, whereas increased used of non-narcotic analgesics was not.

Pain Scoring Instrument and Validation: Patients recorded disease-related pain, using the Present Pain intensity (PPI) scale of the McGill-Melzack questionnaire *[Melzack 1975]* and analgesic use, including the name, strength, and number of pills, daily, in a patient diary. The PPI scale is comprised of 6 verbal descriptors: 0 = no pain; 1 = mild pain; 2 = discomforting pain; 3 = distressing pain; 4 = horrible pain and 5 = excruciating pain. Patients were asked to classify the average pain level during the previous 24 hours. All diaries were collected in a central location and reviewed in a blinded fashion by two independent scorers, who calculated baseline and average weekly PPI and narcotic analgesic scores for all the patients.

The Present Pain Intensity (PPI) scale is one of three components of the McGill Pain Questionnaire (MPQ) *[Melzack 1975]*. Validation studies showed that the MPQ provides quantitative information that can be treated statistically; is sufficiently sensitive to detect differences among different methods to relieve pain; and (using all three elements) provides information on the relative effects of a given manipulation on the sensory, affective, and

evaluative dimensions of pain *[Melzack 1975]*. In examining the statistical relationship between internal MPQ measures, there was a significant correlation between the PPI and all components of the Pain Rating Index *[Melzack 1975]*.

The replicability and consistency of the MPQ for assessment of cancer pain were assessed by single and multiple administrations of the MPQ in 2 patient samples, each comprised for 18 cancer outpatients in pain *[Graham et al 1980]*. Results showed that the MPQ is a reliable measure of immediate pain, but not as a summary measure of past pain over a defined period of time.

As noted above, the use of the PPI score and analgesic score to assess disease-related pain in patients with HRPC and demonstrate the effects of intervention in pivotal studies of mitoxantrone *[Tannock et al 1996]* and docetaxel *[Tannock et al 2004]* for treatment of HRPC provides further validation for use of PPI and analgesic scores in patients with HRPC.

5.5.2 Central Adjudication of Progression Events

Disease progression was first determined by the investigators. If the investigators determined that there was disease progression, then both treatment and progression assessment terminated.

Regardless of the investigator's assessment of disease progression, an Independent Review Committee (IRC) conducted a blinded review of all available radiographic documentation, PPI and analgesic scores, and clinical information from all 950 patients to determine disease progression and timing of disease progression. The IRC review was conducted without knowledge of the investigator's assessments, blood counts, and, except for the first 53 patients, PSA data.

All blinded image assessments and blinded assessments of disease progression were managed by an independent imaging core laboratory (BEACON Bioscience, Inc., Doylestown, Pennsylvania) in compliance with the Independent Review Charter. The Independent Progression Review Process consisted of 2 sequential components:

- First, an Independent Radiology Review of imaging data was performed by 2 independent radiologists (Reader 1 and Reader 2) who separately reviewed all image data. Any discrepancies between the reviewers were adjudicated by a third radiologist (Reader 3);
- Subsequently, all progression events were reviewed by an Independent Progression Panel consisting of 2 medical oncologists, with the adjudicating radiologist (Reader 3) serving in a non-voting consultative role.

All patients were reviewed by the Independent Progression Panel based on pre-specified criteria in the Independent Review Charter. Each possible category for progression was reviewed separately using line listings and the patient was determined to have either shown progression (with an associated date for progression) or no progression for the progression category reviewed. The reviewing oncologists identified the date of each PFS event and specified the type and the date of the earliest PFS event, which was used for the PFS analyses as adjudicated by the IRC.

5.5.3 Validity of Composite Endpoint for Disease Progression

The acknowledged heterogeneity of advanced HRPC argues for the need for a composite endpoint to capture a variety of progression events. Although the protocol-specified composite endpoint used in the SPARC trial has not been used previously in a registration trial, all of the elements involving tumor progression, skeletal related events, and symptomatic progression each have been used in previous registration studies. Radiographic progression based on RECIST criteria has been commonly used for assessment of measurable disease. Pain symptoms, assessed by PPI score and analgesic use, were the basis for approval for mitoxantrone for palliative treatment of patients with symptomatic HRPC. A composite skeletal related events endpoint, defined as observation of any of pathologic fracture, radiation therapy to bone, surgery to bone, spinal cord compression, and, in the case of HRPC, change in antineoplastic therapy due to increased pain, was the basis of approval for two bisphosphonate drugs (pamidronate and zoledronate). As recommended in the FDA Guidance for Industry *"Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format"*, issued January 2006, post-hoc analyses were performed to assess the treatment effect separately for each of the major components in the composite endpoint.

5.6 Prespecified Plans for Analysis of Trial Endpoints

As a result of several discussions with FDA, it was agreed that PFS was an acceptable endpoint for consideration for accelerated approval, provided that the trial was powered for survival. Therefore, the Statistical Analysis Plan (SAP) for the SPARC trial treated PFS and OS as co-primary endpoints, PFS for accelerated approval and OS for full approval. PFS was determined from the day of randomization to the day of first occurrence of radiologic progression, symptomatic progression, skeletal related event, or death from any cause. Time to death in the OS analysis was determined from day of randomization. In addition to the primary endpoints of PFS and OS, the SAP specified a secondary endpoint of time-to-pain progression and exploratory endpoints of pain response, RECIST response for soft tissue or visceral target lesions *[Therasse et al 2000]*, and PSA response according to Working Group criteria *[Bubley et al 1999]*. Pain response was defined as a decrease in average weekly PPI score by 2 points for 5 consecutive weeks, with stable analgesic score.

5.6.1 Sample Size Determination

The trial was powered to detect an improvement in survival with a hazard ratio of 0.77, an overall α of 0.05 split between 2 co-primary endpoints, and a power of 90%, considering a 2:1 (S+P:P) randomization, a median survival time in the placebo group of 12 months, and patient accrual over 24 months. The projected total accrual was 912 patients with 700 events needed for the final OS analysis. A similar number of PFS events were needed to detect an improvement in PFS with a hazard ratio of 0.77 with 90% power in the final PFS analysis.

5.6.2 Analyses and Analytical Tools

Time-to-event endpoints (PFS, OS, and time-to-pain progression) were analyzed using the stratified unadjusted log-rank test. The hazard ratio and the corresponding 95% confidence intervals (95% CI) were generated using the Cox Proportional Hazards model for each of the endpoints. The Kaplan-Meier estimates and associated curves for these time-to-event endpoint also were presented.

Subset analyses were conducted for the following patient subsets:

- Baseline performance status (ECOG 0-1, ECOG ≥2);
- Baseline average PPI score (0, 1- 5, rounded to nearest integer);
- Type of progression after prior chemotherapy (PSA increase only, disease progression);
- Age (<65, ≥65 years);
- Baseline lactate dehydrogenase (LDH) level (<2 x ULN, ≥2 x ULN);
- Baseline hemoglobin (Hgb) level (≥11 g/dL, <11 g/dL);
- Baseline alkaline phosphatase level (<1.5 x ULN, ≥1.5 x ULN);
- Type of prior chemotherapy (docetaxel, other);
- Baseline bisphosphonate use (no, yes);
- Ethnicity (Caucasians, non-Caucasians);
- Geography (North America, outside North America).

For the PFS endpoint, a series of sensitivity analyses were performed as suggested in the FDA Draft Guidance for Industry *"Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics"*.

The SAP also specified that (exploratory) subgroup analyses were to be performed to assess the effect of the type of prior chemotherapy on PFS at final PFS analysis and overall survival on final OS analysis. Additional subgroup analyses were performed for patients with no pain at baseline, patients with pain at baseline, and patients enrolled from North America.

The Fisher Exact test was used for the analyses of proportions.

All analyses were conducted on an intent-to-treat basis, unless otherwise specified. All p-values are 2-sided.

5.6.3 Allocation of Type 1 Error; Interim and Final Analyses

The SAP defined three pre-specified analyses: (1) an interim analysis on PFS to be conducted at 50% (347) of the expected PFS events (and subsequent interim analysis of OS if the difference in PFS reached a pre-specified α threshold), on the basis that the trial was a randomized, placebo-controlled trial that might demonstrate a significant benefit of satraplatin on OS early in the trial; (2) a final analysis on PFS to be conducted when about 700 progression events were observed; and (2) a final analysis on OS when at least 700 deaths were observed.

The overall α error was split equally between PFS and OS, so that the α-level was 0.025 for each of the primary endpoints. Then, the Hochberg-Tamhane *[Hochberg & Tamhane 1987]* and O'Brien-Fleming *[O'Brien & Fleming 1979]* approaches were employed. The Hochberg-Tamhane method was used to address the α-level dependency of the PFS and OS endpoints and to preserve the overall α level and the O'Brien-Fleming method was implemented to correct for multiple looks.

A table of the decision rules and significance levels for declaring success at the pre-specified interim and final analyses for PFS and OS was provided to the Data Monitoring Board (DMB), who assessed results and advised the sponsor (who remained blinded) regarding trial continuation or discontinuation.

To summarize, at the time of the interim PFS analysis, PFS was to be tested using $\alpha = 0.0015$. Whether to carry out the interim analysis on OS at that time was dependent upon a positive interim analysis of PFS. In the case of a significant difference in the interim analysis of PFS, OS was to be tested with $\alpha = 0.0174$. If the interim analysis was not positive, a final analysis of PFS was to be done with the full number of events and $\alpha = 0.0477$, while the α for OS remained at 0.0174. At the time of the final analysis of PFS, if the α was met for PFS, but not for OS, PFS had to be retested using $\alpha = 0.0244$.

The interim PFS analysis, involving 354 PFS events, was conducted based on a cut-off date of 15 June 2005. The interim PFS analysis was considered significant at $\alpha \leq 0.0015$, but the pre-specified level of significance for an interim analysis of OS was not achieved. The DMB informed the sponsor that the trial should proceed as planned, without communicating the results of the interim analyses. The trial remained blinded and the pre-planned final analysis of PFS was undertaken based on a cut-off date of 15 June 2006.

The final PFS analysis involved 802 PFS events with the pre-specified $\alpha = 0.0244$. More than the specified 700 PFS events were included in the final analysis due to the time lag between investigator reported PFS events and data cleaning and blinded IRC review of individual patient data. The final OS analysis will be conducted when at least 700 deaths have been observed and for that analysis an $\alpha = 0.0444$ will be employed.

All data were handled and analyzed by a Contract Research Organization and results of their analysis were reviewed by the DMB prior to unblinding the Sponsor (GPC Biotech).

6. SPARC TRIAL RESULTS

In the SPARC trial *[GPC SAT3-03-01]*, 950 patients with advanced HRPC that had progressed after one prior systemic chemotherapy were randomized 2:1 to treatment with satraplatin (80 mg/m^2/day dx5 q35d) plus prednisone (5 mg bid dx35) (n=635) or placebo plus prednisone (n=315). All patients received prophylactic 5HT3 receptor antagonist (or placebo) antiemetic. Randomization was stratified for performance status (ECOG 0-1 *vs*. ≥2), average baseline PPI score (0-1 *vs.* 2-5), and type of progression after prior chemotherapy (isolated PSA rise *vs*. tumor progression; patients with both tumor progression and PSA progression were stratified as tumor progression).

For early analysis of the SPARC trial, the primary endpoint was PFS, based on a composite endpoint that did not include PSA progression, with progression events and timing adjudicated by a blinded Independent Review Committee (IRC). Secondary endpoints were time-to-pain progression and interim analysis of overall survival. Pre-specified exploratory endpoints for early analysis were pain, tumor, and PSA response rates.

Results from the SPARC trial comprise the primary basis of efficacy and safety of satraplatin for treatment of patients with advanced HRPC that has progressed after first-line chemotherapy. Results from the prematurely terminated EORTC trial *[CA142-025, EORTC 30972; Sternberg et al 2005]* are considered as supportive evidence of efficacy in a closely related population, i.e., men with HRPC who have not previously received chemotherapy.

6.1 Patient Disposition

A total of 950 patients were randomized into the trial, 635 to satraplatin and 315 to placebo, consistent with the planned 2:1 randomization (Table 1). Only 8 patients, 6 (0.9%) randomized to satraplatin and 2 (0.6%) randomized to placebo, failed to receive a single dose of study drug.

As of the 15 June 2006 cut-off date for final analysis on PFS, 112 patients were still on-study, receiving study treatment. A total of 838 (88.2%) patients in the ITT population had discontinued the trial, 545 (85.8%) in the satraplatin arm and 293 (93.0%) in the placebo arm. The most frequent primary reason for trial discontinuation was investigator determined progressive disease, 63.6% in the satraplatin arm and 77.1% in the placebo arm. Discontinuation due to an adverse reaction occurred in 4.3% of the patients in the satraplatin arm and 1.9% of the patients in the placebo arm. Discontinuations due to study drug-related adverse events were higher in the satraplatin arm compared to the placebo arm, but this only affected a small number of patients (2.5% *vs*. 0.6%). Similar percentages of patients in the satraplatin and placebo arms discontinued therapy due to death other than disease progression (0.8% and 1.0% of patients in the satraplatin and placebo arms, respectively), adverse events judged unrelated to study drug (1.7% and 1.3%), withdrawal of consent (6.6% and 5.4%), and other reasons (6.5% and 5.7%). Only 2.0% of patients withdrew due to rising PSA, but other reasons for going off trial could have been based on PSA increased, such as consent withdrawn, patient or investigator decision.

Table 1 Patient Disposition, Intent-to-Treat Population – SPARC Trial

Status	Number (%) of Patients		
	Satraplatin (N=635)	Placebo (N=315)	Total (N=950)
Randomized	635 (100%)	315 (100%)	950 (100%)
Received at least 1 dose of trial medication[a]	629 (99.1%)	313 (99.4%)	942 (99.2%)
Discontinued	545 (85.8%)	293 (93.0%)	838 (88.2%)
On-trial	90 (14.2%)	22 (7.0%)	112 (11.8%)
Primary reason for discontinuation			
Progressive disease	404 (63.6%)	243 (77.1%)	647 (68.1%)
Adverse event	27 (4.3%)	6 (1.9%)	33 (3.5%)
Trial drug related	16 (2.5%)	2 (0.6%)	18 (1.9%)
Other adverse event	11 (1.7%)	4 (1.3%)	15 (1.6%)
Consent withdrawn/Refused treatment	42 (6.6%)	17 (5.4%)	59 (6.2%)
Death	12 (1.9%)	6 (1.9%)	18 (1.9%)
Disease progression	7 (1.1%)	3 (1.0%)	10 (1.1%)
Other causes	5 (0.8%)	3 (1.0%)	8 (0.8%)
Protocol violation	17 (2.7%)	3 (1.0%)	20 (2.1%)
Lost to follow-up	2 (0.3%)	0	2 (0.2%)
Other reasons	41 (6.5%)	18 (5.7%)	59 (6.2%)
PSA elevation	10 (1.6%)	9 (2.9%)	19 (2.0%)
Suspected progression	6 (0.9%)	2 (0.6%)	8 (0.8%)
Patient decision	5 (0.8%)	0	5 (0.5%)
Investigator decision	16 (2.5%)	3 (1.0%)	19 (2.0%)
Sponsor decision	3 (0.5%)	0	3 (0.3%)
Eligibility deviation	0	2 (0.6%)	2 (0.2%)
Protocol non-compliance	1 (0.2%)	1 (0.3%)	2 (0.2%)
Error in evaluation	0	1 (0.3%)	1 (0.1%)

Note: Patient may have had more than 1 reason for discontinuation and only the primary reason for discontinuation was listed.

[a] Reasons for failure to receive trial medication (n=8) included 2 patients who withdrew consent in order to receive alternative treatment (radiation therapy for pain control and mitoxantrone); 1 withdrawn by Sponsor for elevated SGOT on Day 1; 1 who developed spinal cord compression; 1 who had received 2 prior chemotherapy regimens and was taken off trial the same day as randomization; 1 who had prior strontium therapy; 1 who needed a channel cut with radiotherapy; and 1 who failed to meet inclusion criteria and for whom a waiver was not granted.

6.2 Patient Demographics and Background Characteristics

There were no imbalances between the satraplatin and placebo arms in any of the individual parameters analyzed. The majority of patients were Caucasian (88.5%) and 65 years of age or older (71.3%), with ECOG performance status 0-1 (89.3%) and no or minimal pain, reflected by PPI scores of 0-1 (64.1%). Disease progression following prior chemotherapy was mostly based on tumor progression (54.9%) (Table 2).

Prognostic Factors: A relatively small percentage of patients had factors associated with poor prognosis, including hemoglobin <11 g/dL (21.5%), LDH ≥2x ULN (9.4%), alkaline phosphatase ≥1.5x ULN (39.4%), ECOG performance status ≥2 (10.7%), and PPI 2-5 (35.7%). There were no imbalances between treatment arms for these prognostic factors.

Geographic Regions: A total of 170 centers from 16 countries participated in the trial. The largest accruing geographic region was Europe (52.8% of patients), followed by the US (27.2%) and South America (12.7%). The 11 largest accruing sites accounted for 24.3% of patient accruals, but, individually, each accrued only 1.9% to 2.9% of patients: center 285 (Poland) accrued 2.9% of total patients; center 416 (France) 2.6%; center 411 (France) 2.4%; center 452 (Peru) 2.2%, center 502 (Russia) 2.2%; center 278 (Poland) 2.1%; center 480 (UK) 2.1%; center 227 (Hungary) 2.0%; center 486 (UK) 2.0%; and center 003 (US) and center 478 (UK) both 1.9%. Randomization was not stratified by geographic region.

Disease Diagnosis and Staging; Prior Treatment: Characteristics regarding disease diagnosis and staging and prior treatments were balanced between treatment arms. Patients enrolled in the SPARC trial most often had presented with advanced disease at initial diagnosis, with Jewett stage D2 disease (40% of patients) and Gleason scores of 5-7 (44%) or 8-10 (35%). Almost all patients (98%) had received hormonal therapy for their prostate cancer. The majority of patients previously had been treated with surgical procedures (57%) and/or radiotherapy (60%). Slightly over half of patients (51.3%) had received docetaxel-based chemotherapy for metastatic disease and 38% had received prednisone. The median time from disease progression to randomization into SPARC was 4.9 weeks (range: 0.1 to 134.4 weeks).

Concomitant Conditions: There were no obvious imbalances between treatment arms for concomitant conditions, physical findings, and concomitant medications. As might be expected for an elderly population, patients presented with a wide range of ongoing medical conditions in addition to their prostate cancer, the most common including musculoskeletal (55% of patients), cardiovascular (53%), genitourinary (30%), and gastrointestinal (30%) conditions.

Table 2 Selected Demographic & Baseline Characteristics, Intent-to-Treat Population – SPARC Trial

Demographic Characteristic	Number (%) of Patients		
	Satraplatin (N=635)	Placebo (N=315)	Total (N=950)
Age			
≥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%)
Geographic region			
North America[a]	180 (28.3%)	81 (25.7%)	261 (27.5%)
Europe & Israel[b]	372 (58.6%)	196 (62.2%)	568 (59.8%)
South America[c]	83 (13.1%)	38 (12.1%)	121 (12.7%)
Baseline Characteristic			
ECOG Performance Status			
ECOG 0-1	563 (88.6%)	285 (90.5%)	848 (89.3%)
ECOG 2	72 (11.3%)	30 (9.5%)[d]	102 (10.7%)[d]
Average PPI Score[e]			
PPI 0	226 (36.8%)	101 (33.8%)	327 (35.8%)
PPI 1-5	387 (63.0%)	197 (66.0%)	584 (64.0%)
Average Analgesic Score[f]			
>0 (i.e., taking opioids)	261 (41.1%)	128 (40.6%)	389 (40.9%)
>8	123 (19.6%)	51 (17.0%)	174 (18.3%)
Current bisphosphonate use			
No	440 (69.3%)	229 (72.7%)	669 (70.4%)
Yes	195 (30.7%)	86 (27.3%)	281 (29.6%)
Type of progression after prior chemotherapy			
Tumor progression	344 (54.2%)	178 (56.5%)	522 (54.9%)
PSA increase only	290 (45.7%)	136 (43.2%)	426 (44.8%)
Prior anticancer chemotherapy[g]			
Docetaxel	327 (51.5%)	160 (50.8%)	487 (51.3%)
Mitoxantrone	128 (20.2%)	64 (20.3%)	192 (20.2%)

max: maximum; min: minimum; PPI: Present Pain Intensity

[a] Includes US (258 patients accrued) and Canada (3)

[b] Includes Belgium (46 patients accrued), Croatia (24), France (141), Germany (61), Hungary (22), Israel (14), Italy (23), Netherlands (11), Poland (71), Russia (28), Spain (42), and UK (85)

[c] Includes Argentina (98 patients accrued) and Peru (23)

[d] Includes one patient in the placebo group with ECOG PS=3.

[e] For 39 patients with no or incomplete baseline pain diaries , the PPI score for the first week on-trial was used in subsequent assessments and was substituted as baseline PPI by the IRC.

[f] Based only on narcotic analgesics, 10 mg morphine = 2

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

6.3 Efficacy

6.3.1 PFS: Primary Endpoint for Consideration for Accelerated Approval

6.3.1.1 Types of PFS Events

A total of 802 PFS events were observed, 528 (83.1% of patients) in the satraplatin arm and 274 (87.0%) in the placebo arm (Table 3). Radiographic progression and pain progression comprised the majority of PFS events on both satraplatin (70.1% of PFS events) and placebo (79.6%). Comparable proportions of patients had radiographic progression in both arms (35.8% *vs.* 36.9%), but there were fewer pain progressions in the satraplatin arm than in the placebo arm (34.3% *vs.* 42.7%). Patients who died with no IRC defined progression until death, on trial or later, were considered to have death as a PFS event. A somewhat higher proportion of patients in the satraplatin arm had death as a PFS event; however, there was no difference between treatment arms in the incidence of on-study deaths (0.9% vs. 1.8% of patients on satraplatin and placebo, respectively).

Table 3 PFS Events as adjudicated by the IRC, Intent-to-Treat Population – SPARC Trial

	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%)
Bone lesions alone	129/528 (24.4%)	63/274 (23.0%)	192/802 (23.9%)
Soft tissue lesions alone	32/528 (6.1%)	19/274 (6.9%)	51/802 (6.4%)
Bone + soft tissue lesions	27/528 (5.1%)	18/274 (6.6%)	45/802 (5.6%)
Unspecified	1/528 (0.2%)	1/274 (0.4%)	2/802 (0.3%)
Symptomatic progression:	211/528 (40.0%)	132/274 (48.2%)	343/802 (42.8%)
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[1]	58/528 (11.0%)	23/274 (8.4%)	81/802 (10.1%)
No IRC defined progression until death	48/528 (9.1%)	13/274 (4.7%)	61/802 (7.6%)

[1] Includes patients receiving a new chemotherapy or steroids considered by the IRC as evidence of progression.

6.3.1.2 Primary Analysis on PFS

The final analysis on PFS for the ITT population (as adjudicated by the IRC), showed a highly significant 33% reduction in risk of progression for satraplatin compared with placebo (HR=0.67, 95% CI: 0.57, 0.77, p<0.0001). (Fig.1, Table 4). That benefit becomes apparent in the Kaplan-Meier plot after 2 courses of therapy, reflecting the first assessment for radiographic progression. The mean PFS was 24.9 weeks in the satraplatin arm *vs.* 16.2 weeks in the placebo arm, a difference of 8.7 weeks. There was little difference as measured by the medians, 11.1 weeks for the satraplatin arm *vs*. 9.7 weeks in the placebo arm. However, there was a marked difference favoring satraplatin in the percentage of patients who were progression-free at 6 months (30% *vs.* 16% of patients in the satraplatin and placebo arms, respectively) and 12 months (17% *vs.* 7%).

Fig. 1 Kaplan Meier plot of Progression-Free Survival as adjudicated by the IRC, Intent-to-Treat Population – SPARC Trial

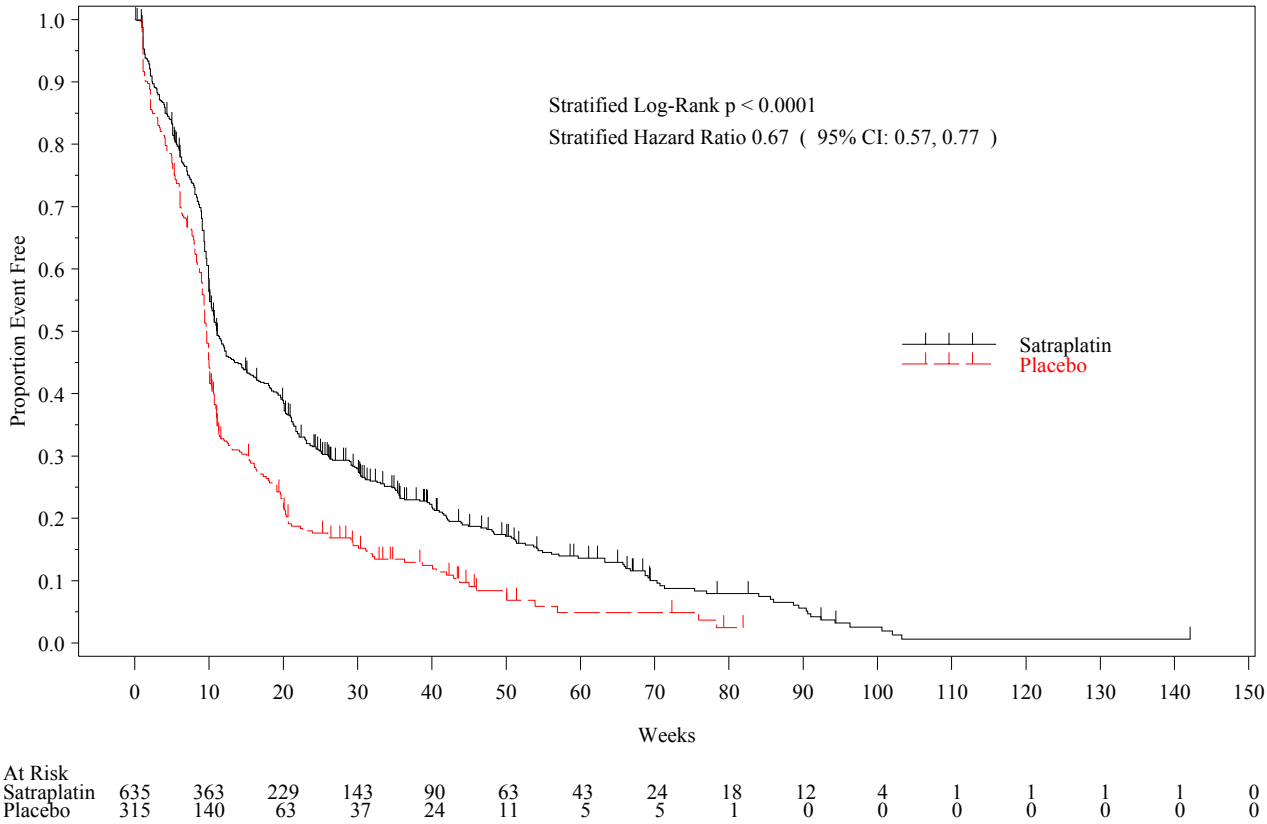


Table 4 Progression-Free Survival as adjudicated by IRC, Intent-to-Treat Population– SPARC Trial

Analysis	Satraplatin (N=635)	Placebo (N=315)	p-value
PFS by IRC – ITT Population			
PFS events (n (%)	528 (83.1%)	274 (87.0%)	<0.0001[a]
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)**		<0.0001[b]

HR: Hazard ratio, CI: confidence intervals, SE: standard error; PFS: progression-free survival
[a]log-rank test
[b]Cox Proportional Hazards model

6.3.1.3 Sensitivity Analyses on PFS

The robustness of the treatment benefit on PFS was demonstrated in 3 ways:

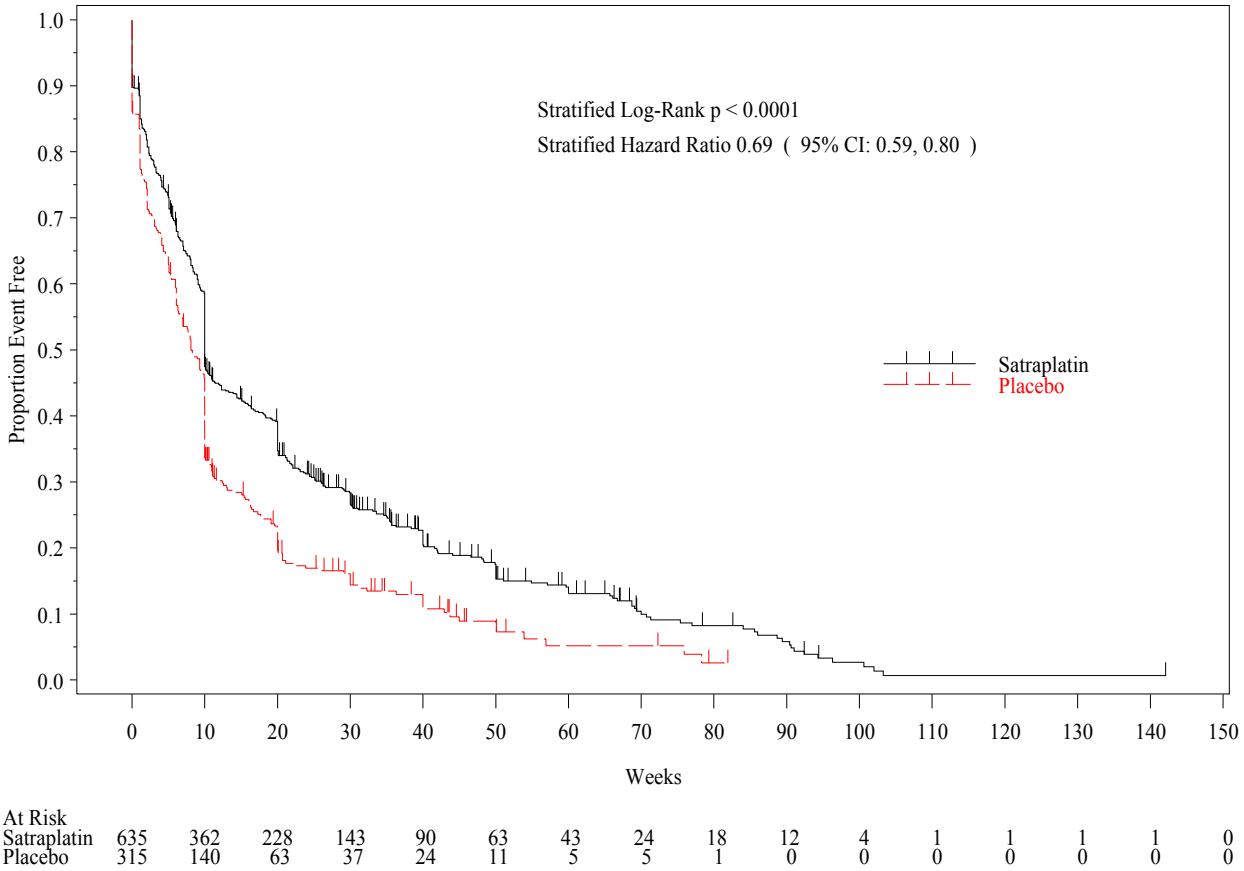
- First, a series of sensitivity analyses were performed to show that the difference in PFS favoring the satraplatin arm remained highly significant after correcting for assessment bias. The first series of analyses assessed progression based only on radiographic assessments or deaths (verified by IRC), reassigning PFS events to fixed assessment dates (next nearest, next earliest, or next latest date); a Kaplan-Meier plot of PFS with fixed dates for radiographic assessments is shown in Fig. 2. Based on finding a 10 day difference in mean time to radiographic assessment between the satraplatin and placebo arms after 6 cycles, another assessment recalculated all PFS dates in the satraplatin arm as if these dates had taken place 10 days earlier. Finally, an analysis of PFS based on investigator assessment yielded a treatment benefit for satraplatin that was of even greater magnitude than the difference observed when the analysis was based on IRC defined PFS events. In all these analyses, the treatment benefits obtained (HR=0.58 to 0.76) were similar to that for the primary analysis on the ITT population (HR=0.67) (Table 5).
- Second, all components of the composite endpoint of PFS yielded results in the same direction. Time-to-event analyses were performed on radiographic progression or death; pain progression or death; and other progression or death. For the two components that comprised 81% of PFS events (including death), the treatment benefits obtained (HR=0.64) were similar to that for the primary analysis on the ITT Population (HR=0.67) (Table 6).
- Third, PFS was also analyzed in a number of subsets of clinical and prognostic significance. The finding of a positive treatment effect of similar magnitude (HR=0.50 to 0.74) in each subset examined supports the conclusion that satraplatin's utility extends across the highly heterogeneous disease spectrum (Fig. 3).

Table 5 Sensitivity Analyses to Assess PFS Robustness, Intent-to-Treat Population– SPARC Trial

Analysis	Satraplatin (N=635)	Placebo (N=315)	p-value
PFS by IRC – ITT Population			
PFS events, n (%)	528 (83.1%)	274 (87.0%)	<0.0001[a]
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)**		<0.0001[b]
Sensitivity Analysis B1 (radiologic events only or death, progression dates reassigned to fixed assessment dates – next nearest)			
PFS events, n (%)	236 (37.2%)	114 (36.2%)	0.002[a]
Mean (SE)	46.0 (2.2) weeks	32.7 (2.5) weeks	
Median	40.1 weeks	20.1 weeks	
HR (95% CI)	**0.70 (0.56, 0.88)**		0.002[b]
Sensitivity Analysis B2 (radiologic events only or death, progression dates reassigned to fixed assessment dates – next earliest)			
PFS events, n (%)	236 (37.2%)	114 (36.2%)	0.003[a]
Mean (SE)	47.1 (2.3) weeks	34.5 (2.8) weeks	
Median	40.1weeks	20.1 weeks	
HR (95% CI)	**0.72 (0.58, 0.91)**		0.005[b]
Sensitivity Analysis B3 (radiologic events only or death, progression dates reassigned to fixed assessment dates – next latest)			
PFS events, n (%)	236 (37.2%)	114 (36.2%)	<0.001[a]
Mean (SE)	46.2 (2.0) weeks	32.6 (2.2) weeks	
Median	40.1 weeks	20.1 weeks	
HR (95% CI)	**0.66 (0.52, 0.83)**		<0.001[b]
Sensitivity Analysis D (satraplatin events shifted by -10 days)			
PFS events, n (%)	528 (83.1%)	274 (87.0%)	0.002[a]
Mean (SE)	23.5 (1.2) weeks	16.2 (1.2) weeks	
Median	9.7 weeks	9.7 weeks	
HR (95% CI)	**0.76 (0.66, 0.89)**		<0.001[b]
Sensitivity Analysis E (progressions based on investigator instead of IRC assessments)			
PFS events, n (%)	497 (78.3%)	275 (87.3%)	<0.001[a]
Mean (SE)	28.6 (1.5) weeks	15.9 (1.2) weeks	
Median	16.0 weeks	6.0 weeks	
HR (95% CI)	**0.58 (0.50, 0.67)**		<0.001[b]

HR: Hazard ratio, CI: confidence intervals, SE: standard error; PFS: progression-free survival
[a]log-rank test
[b]Cox Proportional Hazards model

Fig. 2 Kaplan Meier plot of Progression-Free Survival with radiologic progressions reassigned to fixed assessment dates, Intent-to-Treat Population – SPARC Trial



At Risk																
Satraplatin	635	362	228	143	90	63	43	24	18	12	4	1	1	1	1	0
Placebo	315	140	63	37	24	11	5	5	1	0	0	0	0	0	0	0

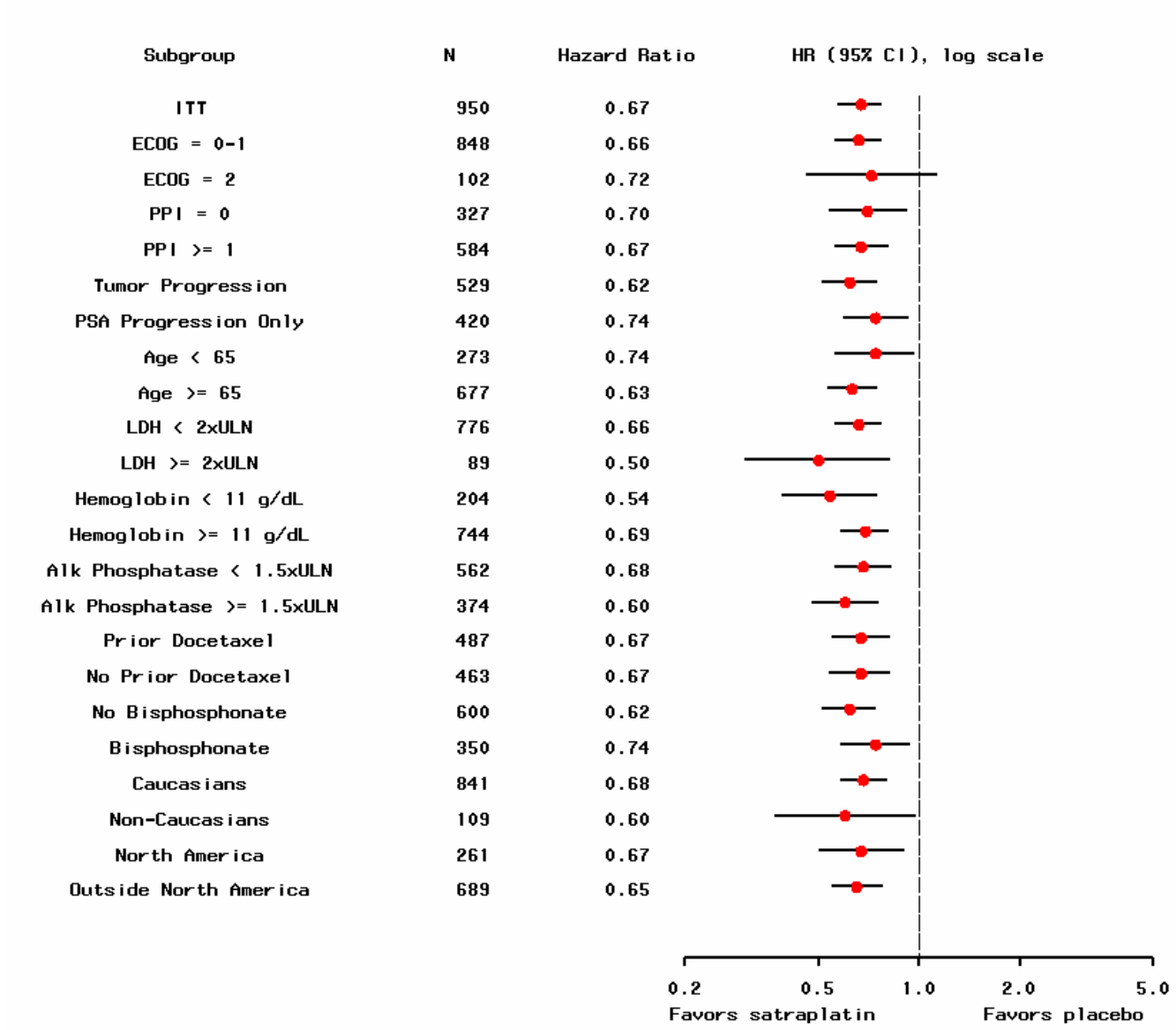
Table 6 PFS by Type of Progression Event, Intent-to-Treat Population – SPARC Trial

Analysis	Satraplatin (N=635)	Placebo (N=315)
PFS – ITT Population		
PFS events, n (%)	528 (83.1%)	274 (87.0%)
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)**	
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 intervals, SE: standard error; PFS: progression-free survival

Fig. 3 Hazard Ratios (and 95% Confidence Intervals) for PFS in Various Prognostic Subsets – SPARC Trial

In the plot below, estimated hazard ratio is depicted by a circle and the 95% confidence interval for the hazard ratio by a horizontal line.



6.3.2 Time-to-Pain Progression

Pain progression was defined as the time from randomization to first observed pain related progression and was determined by the IRC. In the presence of pain progression, patients were not censored for earlier PFS events. In the absence of pain progression, patients were censored on the date of last pain assessment. Analysis of time-to-pain progression for the ITT Population, depicted in Fig. 4 and Table 7, showed a highly significant 34% reduction in risk of pain progression for satraplatin compared to placebo (HR=0.64, 95%CI: 0.51 to 0.79; p<0.0001).

In the satraplatin arm, pain progression events were split about evenly between increased cancer-related pain (52.5%), based on increased PPI score, and increased opioid use (47.5%), based on daily analgesic intake. In the placebo arm, there were more pain progressions based on increased opioid analgesic use (56.2%) than on increased PPI score (43.8%).

As for the PFS analysis, the Cox Proportional Hazards model was used to determine the hazard ratios associated with predetermined covariates in relation to the time to pain progression endpoint. Results showed treatment benefits favoring satraplatin in all subsets examined (HR=0.51 to 0.86) (Figure 5).

Fig. 4 Time to Pain Progression Analysis for the Intent-to-Treat Population – SPARC Trial

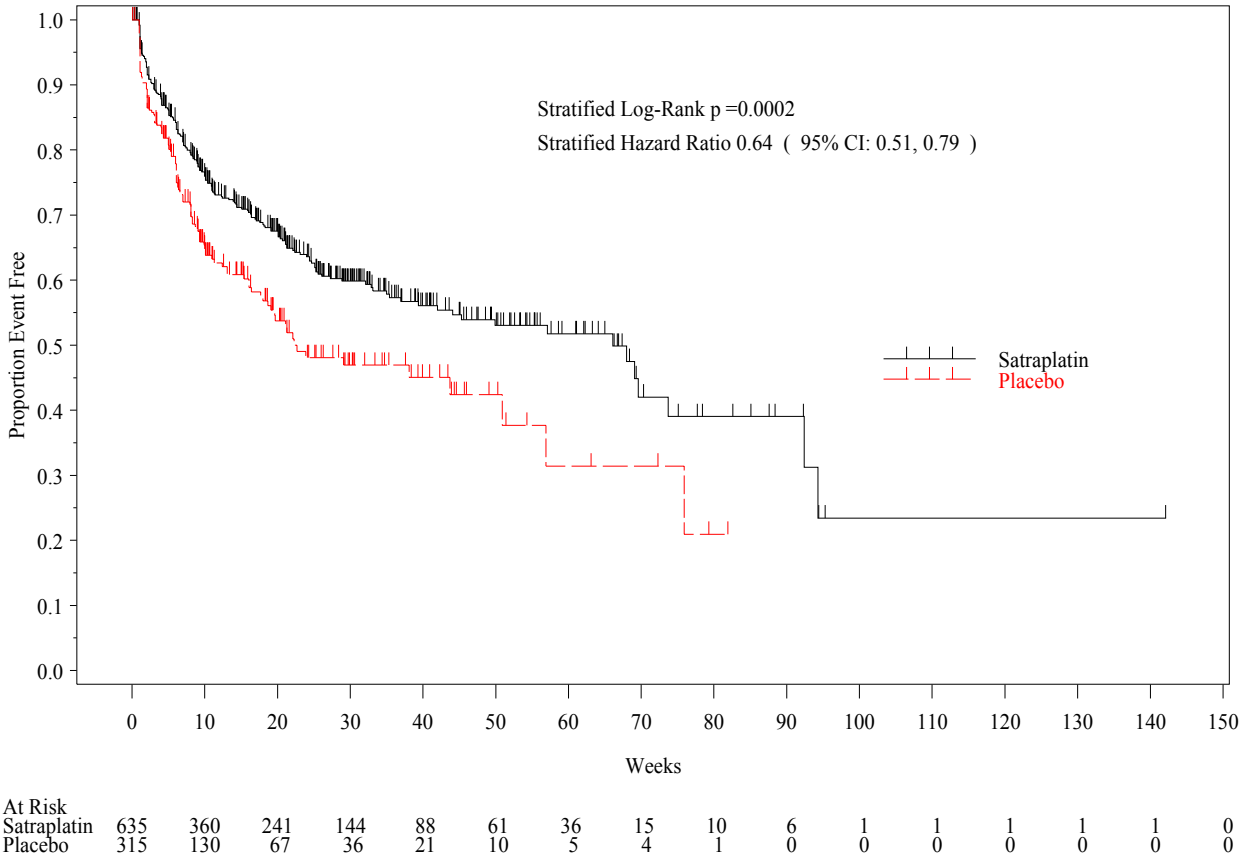


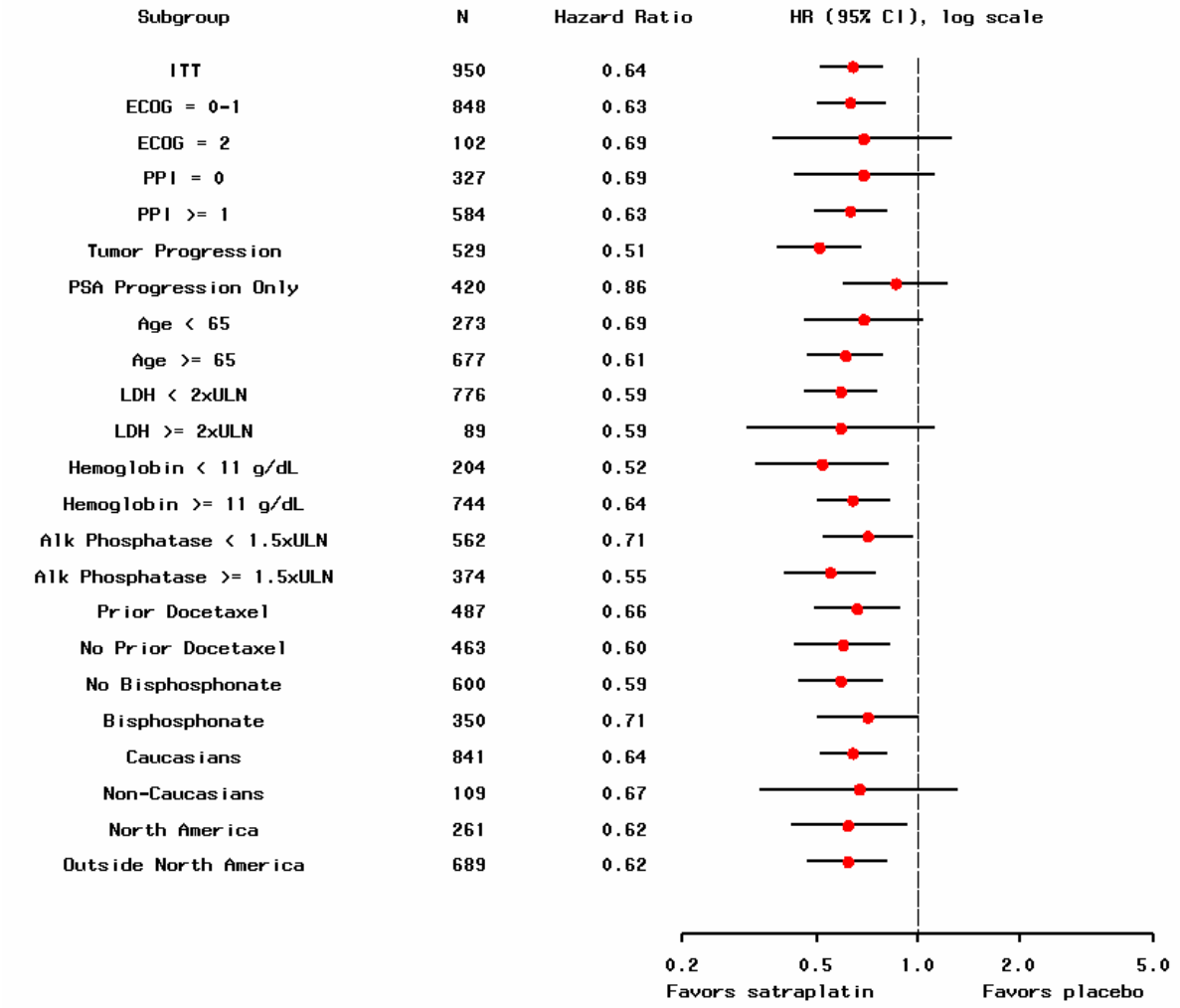
Table 7 Time-to-Pain Progression Analysis, Intent-to-Treat Population – SPARC Trial

Analysis	Satraplatin (N=635)	Placebo (N=315)	p-value
Time to pain progression by IRC – ITT Population			
Pain progression events, n (%)	217 (34.2%)	130 (41.3%)	<0.0001[a]
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)**		<0.0001[b]

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

Fig. 5 Hazard Ratios for Time to Pain Progression in Various Prognostic Subsets – SPARC Trial

In the plot below, estimated hazard ratio is depicted by a circle and the 95% confidence interval for the hazard ratio by a horizontal line.



6.3.3 Exploratory Analyses

6.3.3.1 Pre-Specified Analyses of Tumor, Pain and PSA Response Rates

Results for pre-specified analyses of tumor, pain, and PSA response rates are summarized in Table 8. Response rates were significantly higher in the satraplatin arm compared to the placebo arm for pain response (24.2% *vs*. 13.8% of patients with baseline PPI score 1-5 and at least 4 consecutive weekly assessments of PPI and analgesic score on-trial), RECIST response (6.5% *vs.* 0.6% of patients with target lesions at baseline), and PSA response (25.4% vs. 12.4% of patients with baseline PSA ≥5 ng/mL who experienced ≥50% reduction in PSA from baseline, confirmed by a follow-up test at least 4 weeks later).

Table 8 Pre-Specified Response Rate Analyses, Intent-to-Treat Population – SPARC Trial

Endpoint	Percent (n/N) Patients		p-value
	Satraplatin + prednisone	Placebo + prednisone	
Pain[a]	24.2% (85/351)	13.8% (25/181)	0.005
RECIST[b]	8.0% (22/274)	0.7% (1/134)	0.002
PSA[c]	25.4% (121/476)	11.0% (28/255)	<0.001

n/N: number of patients with response divided by number of patients evaluable for response

[a] Analysis performed for 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 trial medication. Responses were determined by 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.

[b] Response rate based on RECIST criteria among patients with target lesions at baseline. Best overall response was defined as the best response (CR or PR) recorded from the start of treatment until disease progression occurs

[c] Responses defined by ≥50% reduction in PSA from baseline, confirmed by a follow-up test at least 4 weeks later, among patients with baseline PSA of at least 5 ng/mL.

Among patients who experienced a pain response, the median time to pain response was similar in both treatment arms (3.8 *vs*. 3.4 weeks in the satraplatin and placebo arms, respectively). The median duration of pain response was 39.1 weeks on satraplatin *vs*. 24.1 weeks in the control arm (p=0.07).

6.3.3.2 Additional Exploratory Analyses

Additional exploratory analyses were performed to assess pain response and the correlation of pain and disease effect.

Significant treatment benefits for satraplatin were demonstrated both in the percentage of symptomatic patients who became pain-free for at least 5 weeks on-trial without increased analgesic use (OR=1.90, 95% CI: 1.16-3.12) and in the percentage of symptomatic patients who had at least 50% reduction in opioid analgesic use for at least 5 weeks on-trial without increased PPI score (OR=2.89, 95% CI: 1.39-5.99) (Table 9). Note that the 5 week period was selected to correspond with the 5 week course of therapy.

Analyses of pain and analgesic responses by baseline scores showed that the greatest pain benefits were achieved by patients with high baseline PPI scores (PPI 2-5: 18.7% *vs.* 6.7% of patients became pain-free for at least 5 weeks, p=0.0076) and high baseline analgesic scores (analgesic score >8: 20.0% vs. 0% of patients had ≥50% reduction in analgesic use for at least 5 weeks, p=0.0005).

Table 9 Exploratory Pain Analyses– SPARC Trial

	Percent (n/N) Patients		
	Satraplatin + prednisone	**Placebo + prednisone**	**Odds Ratio (95% CI)**
Symptomatic patients becoming pain-free for ≥5 weeks	22.5% (79/351)	13.3% (24/181)	1.90 (1.16-3.12)
Baseline PPI 1	27.7% (41/148)	19.6% (18/92)	
Baseline PPI 2-5	18.7% (38/203)	6.7% (6/89)	
Reduction in analgesic score by ≥50% for ≥5 weeks	26.8% (53/198)	11.2% (10/89)	2.89 (1.39-5.99)
Baseline analgesic score 2-8	35.2% (31/88)	22.2% (10/45)	
Baseline analgesic score >8	20.0% (22/110)	0% (0/44)	

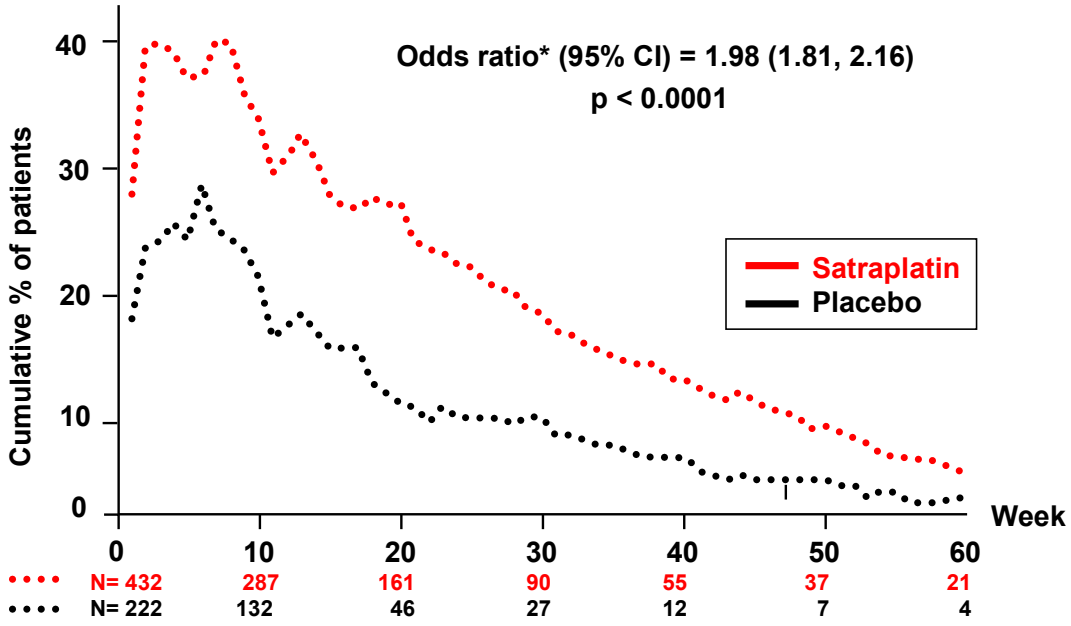
n/N: number of patients with response divided by number of patients evaluable for response

[a] No increased opioid analgesic use

[b] No increased PPI score; 40 mg morphine po = 8

An early treatment benefit on pain was demonstrated in a repeated measures logistic regression analysis of the percentage of patients with ≥50% decrease in PPI score relative to baseline over time (see Fig. 6). A highly significant treatment benefit for satraplatin (OR=1.63, 95% CI:1.51-1.76; p<0.0001) was obvious even during the first 10 weeks of treatment, when there was little separation between treatment arms in the Kaplan-Meier PFS plot.

Fig. 6 Percent of Patients with ≥50% Decrease in PPI Relative to Baseline Over Time – SPARC Trial



An analysis of the percent pain responders by PSA response, summarized in Table 10, showed that the satraplatin-induced pain response most likely resulted from an antitumor effect.

Table 10 Pain Response vs. PSA Response – SPARC Trial

Variable	Percent (n/N) Patients with Pain Response[a]	
	Satraplatin + prednisone	Placebo + prednisone
PSA response[b]	64% (41/64)	33% (5/15)
No PSA response	18% (38/212)	18% (21/114)

n/N: number of patients with response divided by number of patients evaluable for response

[a] Analysis performed for 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 trial medication. Responses were determined by 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.

[b] Responses defined by ≥50% reduction in PSA from baseline, confirmed by a follow-up test at least 4 weeks later, among patients with baseline PSA of at least 5 ng/mL.

6.3.4 Interim Analysis on Overall Survival

The interim analysis on overall survival failed to show a significant difference between treatment arms (Fig. 7 and Table 11). The final analysis on overall survival has not been performed, because the pre-specified number of deaths has not yet been observed.

Fig. 7 Interim Overall Survival Analysis for the Intent-to-Treat Population – SPARC Trial

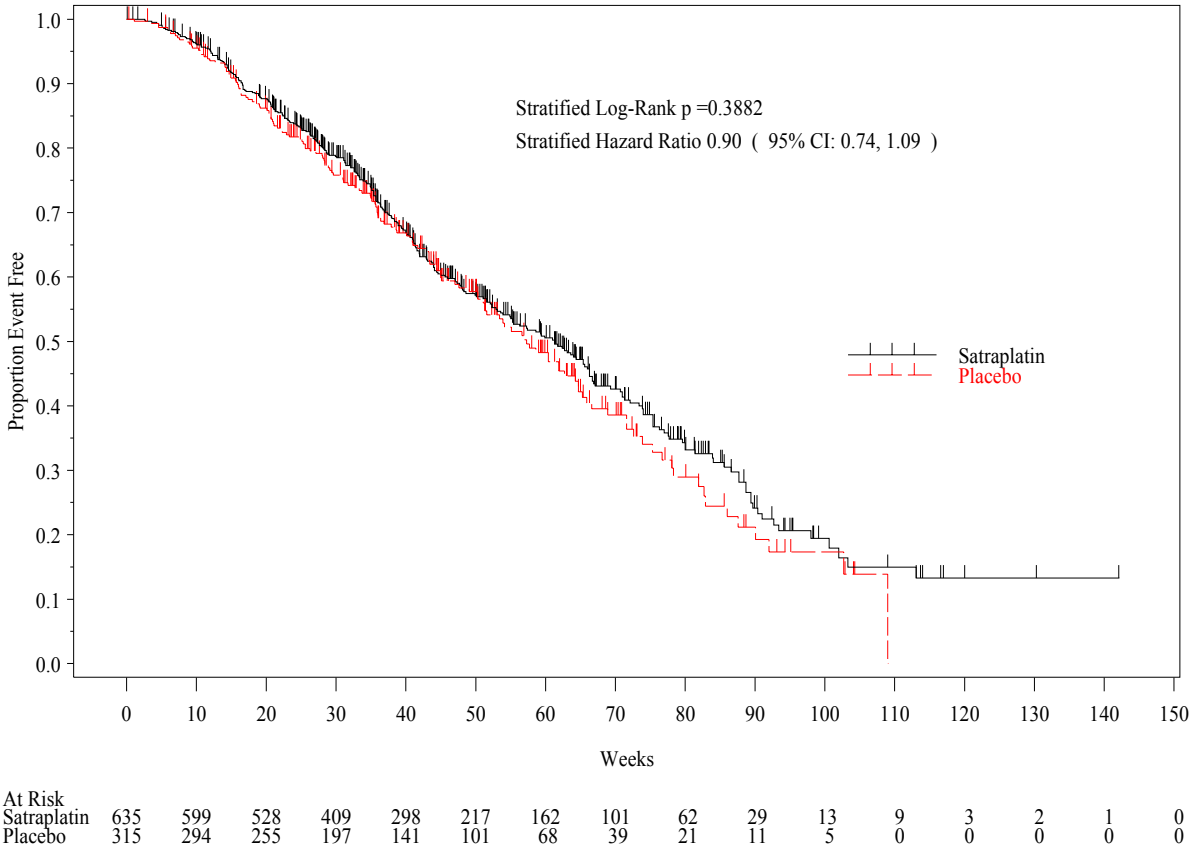


Table 11 Interim Overall Survival Analysis for the Intent-to-Treat Population – SPARC Trial

Analysis	Satraplatin (N=635)	Placebo (N=315)	p-value
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]

HR: Hazard ratio, CI: confidence intervals, SE: standard error
a: log-rank test
b: Cox Proportional Hazards model

At this point, the hazard ratio (HR=0.90) suggests a trend favoring satraplatin. It is assumed that this trend will strengthen as the survival data mature. In support of this speculation, analysis of a population subgroup with more mature survival data, i.e. patients enrolled to 15 June 2005 who had at least 12 months follow-up by the 15 June 2006 cut-off for interim analysis, showed nearly significant treatment benefits on OS, despite being underpowered (p=0.083; HR=0.81; 95% CI: 0.66, 1.01) with a median difference of 9.7 weeks (Fig. 8, Table 12). In spite of all the caveats associated with such analyses, these data suggest there may be a positive outcome on survival with more mature data among the entire ITT population. Note that the Statistical Analysis Plan anticipates that trial participants will have a minimum of 12 months follow-up when the protocol-specified number of death events has occurred for the final analysis on overall survival.

Fig. 8 Interim Overall Survival Analysis for the ITT Subset with ≥12 Months Follow-up- SPARC Trial

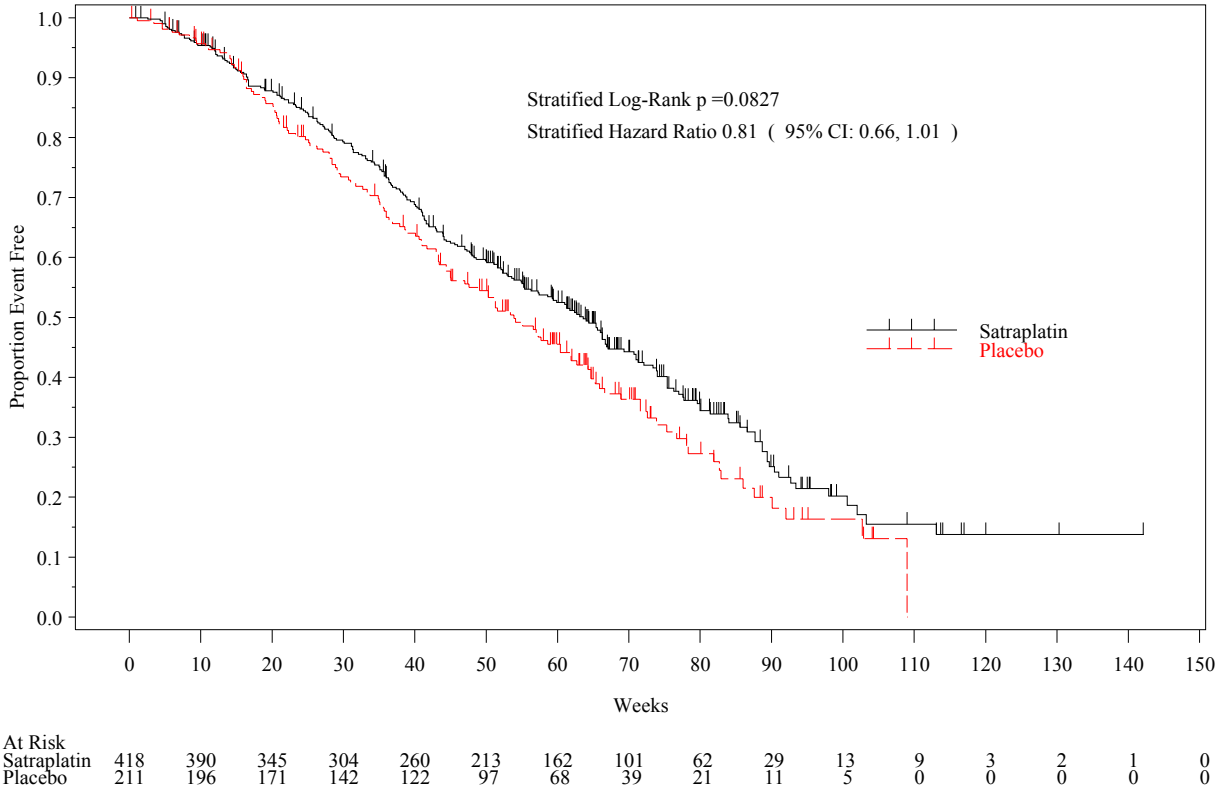


Table 12 Interim Overall Survival Analysis for the ITT Subset with ≥12 Months Follow-up – SPARC Trial

Analysis	Satraplatin (N=418)	Placebo (N=211)	p-value
Death events, n (%)	243 (58.1%)	133 (63.0%)	0.083[a]
Mean (SE)	63.0 (1.9) weeks	56.9 (2.5) weeks	
Median	63.6 weeks	53.9 weeks	
HR (95% CI)	**0.81 (0.66, 1.01)**		0.056[b]

HR: Hazard ratio, CI: confidence intervals, SE: standard error
a: log-rank test
b: Cox Proportional Hazards model

6.3.5 Subset Analyses

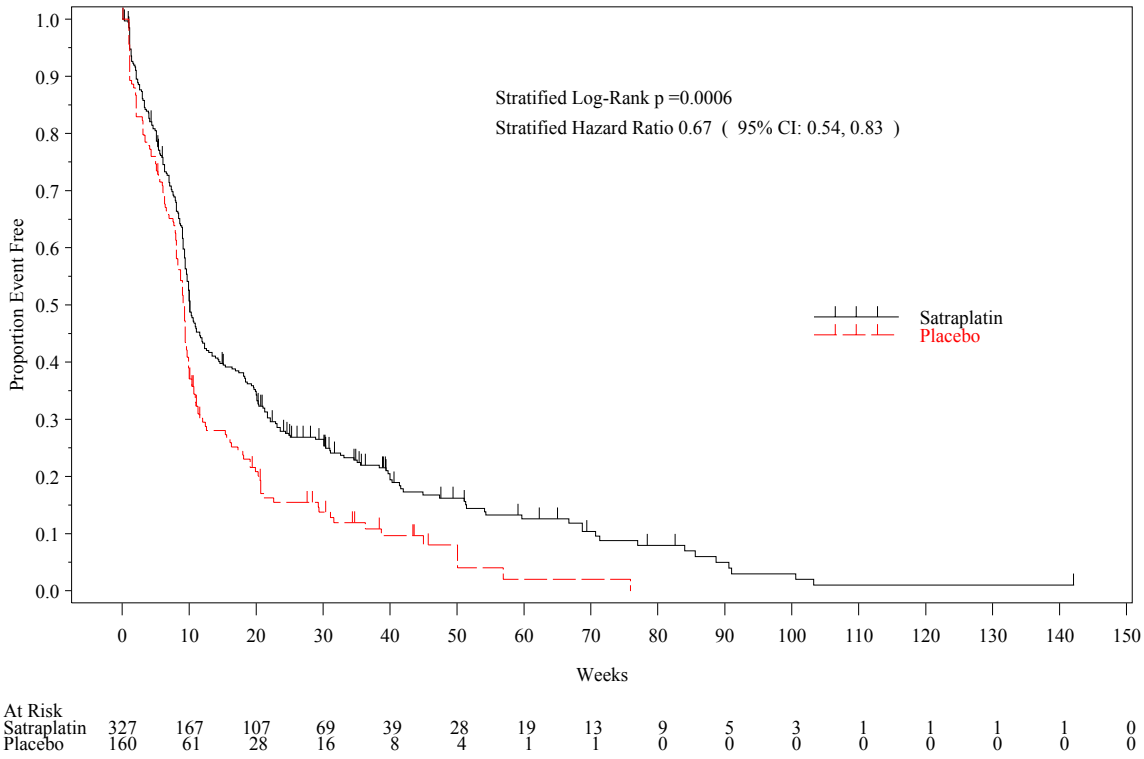
Subset analyses were conducted to compare satraplatin and placebo therapy in terms of PFS, time-to-pain progression and overall survival (Table 13). In each subset examined, satraplatin treatment benefits for PFS (HR=0.67 to 0.70) and time-to-pain progression (HR=0.62 to 0.69) were consistent with those observed for the ITT population. Additionally, the same trend in survival was observed across all subsets.

Table 13 Subset Analyses – SPARC Trial

Population	N	Hazard ratio (95% confidence interval)		
		Progression free survival	Time to pain progression	Overall survival
ITT population	950	0.67 (0.57, 0.77)	0.64 (0.51, 0.79)	0.90 (0.74, 1.09)
Prior docetaxel	487	0.67 (0.54, 0.83)	0.66 (0.49, 0.89)	0.88 (0.67, 1.17)
Baseline PPI 0	327	0.70 (0.54, 0.92)	0.69 (0.43, 1.12)	0.86 (0.57, 1.30).
Baseline PPI 1-5	584	0.67 (0.56. 0.81)	0.63 (0.49, 0.81)	0.90 (0.72, 1.14)
North American patients	261	0.67 (0.50, 0.90)	0.62 (0.42, 0.93)	0.97 (0.66, 1.41)

As an example, the Kaplan-Meier plot for PFS for the subset with prior docetaxel, shown in Fig. 9, is essentially superimposable with that for the ITT population.

Fig. 9 Kaplan Meier plot of Progression-Free Survival as adjudicated by the IRC, Prior Docetaxel Subset – SPARC Trial



6.4 Safety

A total of 942 patients, 629 in the satraplatin arm and 313 in the placebo arm, received at least one dose of trial medication and were included in the safety patient population. Eight patients, 6 in the satraplatin arm and 2 in the placebo arm, were randomized but never received trial medication, so were not included in the safety evaluation. The safety information summarized below is summarized from the 120-day safety update submitted to the NDA, with a cut-off date of 15 November 2006.

6.4.1 Exposure

The satraplatin arm had greater drug exposure than the placebo arm, based on a median of 4 cycles (range: 1-32) compared to 2 cycles (range: 1-19) of treatment, respectively, at median relative dose intensity of 93.8% and 96.4%, respectively, relative to the planned dose (Table 14).. The total median exposure to prednisone was 1.7-fold higher for the satraplatin arm compared to the placebo arm (1270 *vs*. 730 mg), consistent with the median of 4 vs. 2 cycles for the satraplatin and placebo arms, respectively. Only the satraplatin arm was exposed to granisetron, with a median exposure of 39 mg.

Among patients receiving at least one dose of trial drug (satraplatin or placebo), 11.9% in the satraplatin arm and 15.0% in the placebo arm received only one cycle or less of treatment. The most common reason for discontinuing within a single cycle of treatment was pain progression. The early discontinuations due to pain progression resulted from the Sponsor's instructions to the investigators to strictly follow the pain progression rules, even though several advisors argued that trial drug would not have had a chance to exert its effect during the first cycle of treatment.

Dose modifications of trial drug were more frequent in the satraplatin arm than in the placebo arm. Doses were decreased for 21.0% of the patients randomized to the satraplatin arm compared to <1% of those randomized to the placebo arm. Cycle delays ≥7 days were experienced at least once by 44.4% of the patients randomized to receive satraplatin therapy compared to 10.5% of those randomized to receive placebo control.

Dose modifications of prednisone were similar in both the satraplatin and placebo arms. In both treatment arms, about 1/3 of patients had reduction in the prednisone dose, presumably due to prednisone-related toxicity.

Approximately 97% of patients in both the satraplatin and placebo arms received at least one concomitant medication during the SPARC trial. The classes of concomitantly administered medications were given at similar frequencies in both treatment arms, with the exception of greater use in the satraplatin arm compared to the placebo arm for antibacterials for systemic use (23.8% *vs.* 14.7% of patients), antacids (23.1% *vs.* 9.3%), laxatives (15.6% *vs.* 10.2%), antianemic preparations (14.0% *vs.* 4.8%), antithrombotic agents (10.3% *vs.* 4.2%), and beta-blocking agents (6.5% *vs.* 2.6%). Some of these differences could be accounted for by treatments for the complications associated with satraplatin induced myelosuppression, the gastric effects of more prolonged exposure to prednisone, and the constipation induced by granisetron. Of note, only 8.4% and 5.1% of patients in the satraplatin and placebo arms, respectively, received additional antiemetics.

Table 14 Selected Dosing Information,[a] Population Randomized and Treated – SPARC Trial

Variable	Satraplatin + Prednisone + Granisetron (N=629)	Placebo + Prednisone + Placebo antiemetic (N=313)
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/m^2)	132 (21.0%)	1 (0.3%)
Dose increase (>90 mg/m^2)	51 (8.1%)	32 (10.2%)
Dose delay ≥7 days	279 (44.4%)	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 treatment 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)	217 (34.5%)	100 (31.9%)
Dose increase (≥15 mg)	5 (0.8%)	1 (0.3%)
Interrupted cycle	55 (8.7%)	12 (3.8%)
Granisetron/Placebo Administration		
Number of treatment 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

6.4.2 Treatment-Emergent Hematologic Events

Hematologic events were evaluated by assessment of hemoglobin levels and blood cell counts, in accordance with NCI Common Toxicity Criteria (CTC), version 2.0. Hematologic events (worst grade reported) were examined per patient and per cycle (Table 15). Results can be summarized as follows:

- Anemia: The percentage of patients with low hemoglobin was significantly higher in the satraplatin arm than in the placebo arm analyzed both per patient (Grade ≥1: 96.2% *vs*. 90.1%, p<0.001; Grade 3-4: 9.4% *vs*. 3.2%, p<0.001) and per cycle, which normalized for the increased exposure of the satraplatin arm compared to the placebo arm (median of 4 *vs*. 2 cycles of treatment). Grade 3-4 abnormalities were uncommon, but they were seen twice as often in satraplatin cycles compared to placebo cycles (2.8% *vs*. 1.1%, p<0.001).

  Of note, a majority of patients in both treatment arms were anemic at trial entry (hemoglobin Grade 1-3: 76.5% (479/626) *vs*. 74.9% (233/311) of satraplatin and placebo patients, respectively, at baseline).

- Thrombocytopenia: The percentage of patients with low platelet counts was significantly higher in the satraplatin arm than in the placebo arm analyzed both per patient (Grade ≥1: 87.4% *vs*. 19.8%, p<0.001; Grade 3-4: 21.8% *vs*. 1.3%, p<0.001) and per cycle (Grade ≥1: 70.5% *vs*. 11.1%; Grade 3-4: 8.3% *vs*. 0.3%). However, only two satraplatin patients experienced Grade 4 thrombocytopenia.

  Platelet counts <100,000/mm^3 were found in 40.9% (1286/3142) of cycles with platelet values in the satraplatin arm. Relative to the first day of the affected treatment cycle, platelets decreased to <100,000/mm^3 at a median of 26 days and platelet nadirs occurred at a median of 28 days. Platelet counts recovered to >100,000/mm^3 at a median of 35 days. Platelet counts recovered within 6 weeks from the start of the affected treatment cycle in 81.8% (1052/1286) of cycles with thrombocytopenia. Delayed recovery did not appear to be cumulative.

- Leukopenia: The percentage of patients with leukopenia was significantly higher in the satraplatin arm than in the placebo arm analyzed both per patient (Grade ≥1: 76.3% *vs.* 13.7%, p<0.001; Grade 3-4: 13.7% *vs*. 0.6%, p<0.001) and per cycle (Grade ≥1: 54.1% *vs*. 7.7%; Grade 3-4: 3.7% *vs*. 0.3%).

- Neutropenia: The percentage of patients with neutropenia was significantly higher in the satraplatin arm than in the placebo arm analyzed both per patient (Grade ≥1: 66.8% *vs*. 4.8%, p<0.001; Grade 3-4: 21.1% *vs*. 0.6%, p<0.001) and per cycle (Grade ≥1: 38.3% vs. 2.0% of cycles; Grade 3-4: 5.9% *vs*. 0.3%).

  Neutrophil counts decreased to <1500/mm^3 in 19.4% (608/3135) of cycles with neutrophil values in the satraplatin arm. Relative to the first day of the affected treatment cycle, ANC decreased to <1500/mm^3 at a median of 24.5 days and ANC nadirs occurred at a median of 29 days. ANC recovered to ≥1500/mm^3 at a median of 33 days. Neutrophil counts recovered within 6 weeks from the start of the affected treatment cycle in 81.7% (497/608) of cycles with neutropenia. Delayed recovery did not appear to be cumulative.

Table 15 Hematologic Events per Patient and per Cycle (worst grade reported), Population Randomized and Treated – SPARC Trial

	Number (%) of Patients			Number (%) of Cycles		
Laboratory 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.
NS: not significant

The rate of transfusions was significantly higher (p<0.001) in the satraplatin arm for both red blood cell (RBC) transfusions (16.2% *vs*. 8.0%) and platelet transfusions (4.0% *vs*. 0.3%). (Table 16). An examination of transfusion rates by geographic region showed that rates of both RBC and platelet transfusions were higher in North America (RBCs and platelets administered to 18.2% and 5.1% of patients, respectively) and South America (18.1% and 3.6%) and lower in Europe/Israel (14.9% and 3.5%).

Table 16 Incidence of Transfusions, Population Randomized and Treated – SPARC Trial

Transfusion	Number (%) of Patients			Number (%) of Cycles		
	Satraplatin (N=629)	Placebo (N=313)	p-value	Satraplatin (N=3199)	Placebo (N=1179)	p-value
Red blood cells	102 (16.2)	25 (8.0)	<0.001	171 (5.3)	32 (2.7)	<0.001
Platelets	25 (4.0)	1 (0.3)	<0.001	25 (0.8)	1 (0.1)	0.002

6.4.3 Treatment-Emergent Non-Hematologic Events

Most patients experienced at least one non-hematologic treatment-emergent adverse event (TEAE,) but the incidence was significantly higher in the satraplatin arm compared to the placebo arm (91.9% vs. 82.7%, p<0.001). Individual non-hematologic TEAEs (MedDRA Preferred Term) per patient with a significantly higher incidence in the satraplatin arm compared with the placebo arm are summarized in Table 17. Notably, the incidence per patient of satraplatin-related non-hematologic Grade 3-4 events was lower than typical for cytotoxic chemotherapy agents. Briefly:

- Gastrointestinal Disorders: Gastrointestinal disorders were the most frequent non-hematologic TEAEs. Twice as many patients in the satraplatin arm compared to the placebo arm (58.5% *vs*. 29.1%, p<0.001) experienced gastrointestinal events, including constipation (22.9%), diarrhea (24.8%), nausea (29.1%), and vomiting (16.5%). However, only a few patients in the satraplatin arm experienced Grade 3-4 diarrhea (1.9%) and vomiting (1.6%) and there was no significant difference between treatment arms in the incidence of Grade 3-4 constipation (1.9%) and nausea (1.3%);
- Fatigue/Asthenia: A significantly higher percentage of patients in the satraplatin arm compared to the placebo arm experienced fatigue (18.3% *vs*. 11.2%, p=0.005) and asthenia (15.3% *vs*. 9.3%, p=0.011). However, there was no significant difference between treatment arms in the incidence of Grade 3-4 asthenia (3.3%) and fatigue (1.7%);
- Pulmonary events: A significantly higher percentage of patients in the satraplatin arm compared to the placebo arm experienced dyspnea (7.2% *vs*. 3.5%, p=0.028), cough (6.0% *vs*. 2.2%, p=0.009), and pulmonary embolism (1.6% vs. 0%, p=0.036). However, the two treatment arms had the same incidence of Grade 3-4 dyspnea (1.0%) and there were no reports of Grade 3-4 cough;
- Infections: A significantly higher percentage of patients in the satraplatin arm compared to the placebo arm had infectious episodes (23.7% *vs*. 11.5%, p<0.001), including Grade 1-2 upper respiratory tract infections (2.7% *vs*. 0.6%, p=0.046) and Grade 1-2 influenza (1.4% *vs*. 0, p=0.034);

Table 17 Treatment-Emergent Non-Hematologic Adverse Events[a] per Patient (worst grade reported) with Significantly Higher Incidence in Patients Receiving Satraplatin Compared with Placebo, Population Randomized and Treated – SPARC Trial

	Number (%) of Patients, worst grade reported					
MedDRA	All Grades[b]			Grade 3-4[b]		
System Organ Class & Preferred Term	Satraplatin (N=629)	Placebo (N=313)	p-value[c]	Satraplatin (N=629)	Placebo (N=313)	p-value[c]
Patients with any TEAE	578 (91.9%)	259 (82.7%)	<0.001	343 (54.5%)	94 (30.0%)	<0.001
Gastrointestinal disord.	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]TEAEs, coded by MedDRA v. 6.0 and presented by System Organ Class and Preferred Term
[b]NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 2.0
[c]Fisher's exact test; NS: no significant difference in incidence in satraplatin group compared to placebo group
Investigations related to hematologic toxicities not included

- Deep vein thrombosis: Deep vein thrombosis was reported for 10 (1.6%) patients on satraplatin therapy and none on placebo.

Additional retrospective analyses were performed to explore events of special interest, defined by pooling TEAEs coded by MedDRA Preferred Terms from various System Organ Classes. Results from analyses on a per patient basis showed a significantly higher incidence in the satraplatin arm compared to the placebo arm for myelosuppression (61.7% *vs*. 14.7%, p<0.001), asthenia (31.6% *vs.* 19.8%, p<0.001), gastrointestinal toxicity (58.5% *vs*. 29.1%, p<0.001), bleeding/bruising (9.7% *vs.* 4.5%, p=0.005), fever (10.2% *vs.* 5.8%, p=0.027), pulmonary abnormalities (8.1% *vs.* 4.2%, p=0.027) and thrombosis (4.3% *vs.* 0.0%, p<0.001). For Grade 3-4 pooled TEAEs, there was a significant difference between treatment arms only for myelosuppression (30.5% *vs.* 5.4%, p<0.001), gastrointestinal toxicity (7.8% *vs*. 2.2%, p<0.001), and thrombosis (1.7% *vs.* 0.0%, p=0.020).

Results from analyses on a per cycle basis, no longer showed a significant difference between treatment arms in the incidence of bleeding/bruising and pulmonary abnormalities.

As defined by the combined MedDRA Preferred Terms used for this analysis, analyzed either by patient or by cycle, there were no significant differences between the satraplatin and placebo arms in the incidence of hepatic events, renal events, and neuropathy. It should be noted that the incidence of thrombosis in the satraplatin arm (4.3% of patients) was consistent with the rate of thrombosis reported in the literature of patients with cancer treated with chemotherapy *[Haddad & Green 2006; Lee & Levine 2003]*.

6.4.4 Serious Adverse Events & Other Significant Adverse Events

6.4.4.1 Deaths On-Study

A total of 40 (4.2%) patients, 26 (4.1%) on satraplatin and 14 (4.5%) on placebo, died within 30 days of the last dose of study drug or had a TEAE with an outcome of death. The primary cause of most of these deaths, as attributed by investigators, was disease progression, accounting for 69% (18/26) of satraplatin on-study deaths and 57% (8/14) of placebo on-study deaths. Cardiovascular disease, including cerebrovascular accident/stroke, cardiac arrest, cerebral hemorrhage, congestive heart failure, and myocardial infarction, was the second leading cause of death, accounting for 19% (5/26) on satraplatin on-study deaths and 21% (3/14) of placebo on-study deaths. The incidence of cardiovascular deaths was similar in both treatment arms (0.8% *vs.* 1.0% of satraplatin and placebo patients, respectively). The remaining on-study deaths were due to renal insufficiency (2) and squamous cell carcinoma (1) in the satraplatin arm and pleural effusion (1), cervical injury from fall (1), and death during sleep (1) in the placebo arm.

6.4.4.2 TEAEs Resulting in New or Prolonged Hospitalization

TEAEs resulting in new or prolonged hospitalization were reported for 207 (22.0%) patients, 159 (25.3%) on satraplatin and 48 (15.3%) on placebo. Review of patient listings indicated that 40% (64/159) of the hospitalizations for patients receiving satraplatin were caused by myelosuppression, gastrointestinal disorders and/or infections. In the satraplatin arm, individual TEAEs requiring new or prolonged hospitalizations in ≥1% of patients consisted of infectious episodes (pooled, 3.5%), anemia (3.2%), thrombocytopenia (1.4%), spinal cord compression (1.1%), dyspnea (1.0%), pulmonary embolism (1.0%), nausea (1.0%), and dehydration (1.0%).

6.4.4.3 TEAEs Resulting in Discontinuation of Study Drug

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. Events related to underlying disease, including prostate cancer metastases, arthralgia, bone pain, back pain, and spinal cord compression, accounted for 41 (6.5%) satraplatin and 22 (7.0%) placebo discontinuations. Other major causes of satraplatin discontinuations were drug-related myelosuppression in 14 (2.1%) patients and gastrointestinal events in 13 (2.1%) patients.

6.4.4.4 TEAEs Resulting in Delayed Dosing of Study Drug

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.

6.4.4.5 TEAEs Resulting in Dose Reductions

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.

6.4.5 Non-Hematologic Laboratory Abnormalities

Evaluation of liver function tests (ALT/SGPT, albumin, alkaline phosphatase, AST/SGOT, and bilirubin), renal function tests (creatinine, potassium, sodium, uric acid), and metabolic function tests (calcium, glucose, phosphate) showed no significantly increased incidence of laboratory abnormalities in the satraplatin arm compared to the placebo arm, with the following exceptions:

- Hyperbilirubinemia: The incidence of hyperbilirubinemia was significantly higher in the satraplatin arm compared to the placebo arm, analyzed on both a per-patient basis (10.0% *vs*. 3.5% of patients, $p<0.001$) and a per cycle basis (3.3% *vs*. 2.1% of cycles, $p=0.045$). Most of the bilirubin elevations on satraplatin were Grade 1 severity (74.6% or 47/63 patients) and most were transient and rapidly reversible;
- Hypocalcemia: The incidence of hypocalcemia was significantly higher in the satraplatin arm compared to the placebo arm, analyzed on both a per-patient basis (33.7% *vs.* 24.3% of patients, $p=0.003$) and a per-cycle basis (13.4% *vs*. 10.5% of cycles, $p=0.012$). Most of the calcium decreases on satraplatin were Grade 1 severity (75.0% or 159/212 patients). A separate analysis showed that the incidence of hypocalcemia on-trial was significantly higher among patients taking bisphosphonates on-trial compared to those not taking bisphosphonates, regardless of treatment arm (38.2% *vs*. 25.8%, $p<0.001$);
- Hypoalbuminemia: Although a significantly higher percentage of patients in the satraplatin arm compared to the placebo arm experienced hypoalbuminemia over all cycles (34.0% *vs.* 25.9% of patients, $p=0.011$), there was no significant difference between treatment arms on a per-cycle basis (14.2% *vs*. 13.1% of cycles). Most of the albumin decreases on satraplatin were Grade 1 severity (81.3% or 174/214 patients);

- Hyperglycemia: There were more patients with hyperglycemia in the satraplatin arm (51.2% *vs*. 43.5% of patients on satraplatin and placebo, respectively, p=0.027), which may be related to greater exposure to prednisone.

Interestingly, results showed a significantly *lower* incidence per cycle in the satraplatin arm compared the placebo arm for the following laboratory parameters analyzed on a per cycle basis: alanine transaminase elevated (6.5% vs. 8.7% of satraplatin and placebo cycles, respectively, p=0.014); alkaline phosphatase elevated (37.7% *vs*. 44.7% of cycles, p<0.001); creatinine elevated (8.5% *vs*. 11.3% of cycles, p=0.006); and hyperkalemia (3.9% vs. 5.8% of cycles, p=0.010).

6.4.6 Other Observations

6.4.6.1 Electrocardiograms

In the SPARC trial, investigators reported significant abnormalities in at least 1 ECG for 49 (7.8%) satraplatin patients and 15 (4.8%) placebo patients. Significant abnormalities at baseline screening were reported for 31 (4.9%) satraplatin patients and 9 (2.9%) placebo patients.

A review of a subset of SPARC patients was performed in blinded fashion by a board-certified cardiologist who followed the recommendations for analysis of ECG data from clinical trials specified in ICH Guidance E14 *"Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs"*. In order to perform such a review with a manageable subset of patients, ECGs from all eligible patients from US Oncology (USO) sites were reviewed. To be eligible, a patient needed to have baseline ECG and at least one follow-up ECG while on trial. Per protocol, follow up ECGs were scheduled to be performed every other cycle. Based on this criterion, patients with less than two cycles were not eligible and this resulted in a higher number of satraplatin arm patients in the blinded review. Of 118 USO patients randomized for SPARC, 71 were eligible: 56 in the satraplatin arm, 15 in the placebo arm. Of these 71 patients, fourteen patients had QT prolongations by either the Fridericia or the Bazett correction method, including 2 in the placebo arm.

It is likely that the observed difference between treatment arms in QTc prolongations in the subset of USO patients is *not* clinically meaningful because (1) the subset analyzed was small and unbalanced for treatment and exposure; (2) no cardiac events were reported for the 14 patients with observed QTc prolongations; (3) for the entire safety population, there were no significant differences between treatment arms in investigator-reported clinically significant ECG abnormalities at baseline (4.9% vs. 2.9% of patients in the satraplatin and placebo arms, respectively, p=0.171) and on-trial (7.8% vs. 4.8%, p=0.099); and (4) for the entire safety population, there were no significant differences between treatment arms in the incidence on-trial (within 30 days after the last dose of satraplatin or placebo) of individual clinical events characteristic of an effect on QT/QTc, such as torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures. However, among all entries in the SPARC trial, there was a higher incidence in the satraplatin arm of syncope/syncope vasovagal (9 (1.4%) *vs*. 0 patients on the satraplatin and placebo arms, respectively) and ventricular/ supraventricular tachycardia (4 (0.6%) *vs.* 0 cases).

Of note, nonclinical data indicate that satraplatin has no toxic effects on cardiac function. Neither satraplatin nor its main metabolite JM-118 (at concentrations up to 100 μM) had significant

effects on the hERG mediated potassium current. A GLP trial performed with conscious dogs implanted with radiotelemetry transmitters and dose orally at 4.5 mg/kg (90 mg/m^2) as well as anesthetized dogs dosed intraduodenally at 22.5 mg/kg (450 mg/m^2) did not reveal any cardiovascular effects due to satraplatin.

6.4.6.2 Vital Signs and Physical Findings

A total of 453 patients, 299 (47.5%) in the satraplatin arm and 154 (49.2%) in the placebo arm, had at least one abnormality reported in on-trial physical examinations. Investigators considered these physical findings to be clinically significant in 118 (18.8%) satraplatin and 57 (18.2%) placebo patients. Both total and clinically significant findings occurred with similar frequency in both treatment arms.

6.4.6.3 Drug-Drug Interactions

Satraplatin is a strong inhibitor of CYP 3A4, 2C8, 1A1, 1A2, 2A6, 2E1 and 2D6 *in vitro*. Patients participating in the SPARC trial who were receiving concomitantly administered medications with a significant dependency on CYP metabolism for elimination were monitored for drug-specific toxicities. For the four medications prescribed most often to patients in the SPARC trial, there was no significant difference in the frequency of adverse events by treatment arm (Table 18). This suggests there was not a clinically significant effect of satraplatin on the pharmacokinetics of the concomitantly administered medication. These results must be interpreted cautiously, however, due to the small sample size and the retrospective nature of the analysis.

Table 18 Incidence of Concomitant Medication (Conmed) Adverse Effects by Treatment Arm, Population Randomized and Treated – SPARC Trial

Conmed	Metabolizing Enzyme	Adverse Effect	Number of Patients Receiving Conmed by Treatment Arm		Number (percent) of Conmed Treated Patients Exhibiting Adverse Effect	
			Satraplatin	Placebo	Satraplatin	Placebo
Fentanyl	CYP 3A4	Psychiatric Disorder	91	46	12 (13.2%)	5 (10.9%)
Tramadol	CYP 3A4 CYP 2D6	Psychiatric Disorder	90	48	5 (5.6%)	2 (4.2%)
Simvastatin, Atorvastatin	CYP 3A4	Muscle Pain	68	32	20 (29.4%)	6 (18.8%)
Warfarin	CYP 2D6	Bleeding	40	20	7 (17.5%)	2 (10.0%)

7. SUPPORTIVE EFFICACY AND SAFETY INFORMATION

7.1 Supportive Efficacy Information

The persuasiveness of results from the internally consistent, strong, multicenter SPARC trial is supported by results from the EORTC trial in a different phase of disease. The EORTC trial *[CA142-025, EORTC 30972; Sternberg et al 2005]* was a Phase III, international, multicenter, randomized, open-label trial in which patients with advanced HRPC who had not previously received cytotoxic chemotherapy were randomized 1:1 to treatment with satraplatin (100 mg/m^2 po dx5 q35d) plus prednisone (10 mg bid) or prednisone alone. The trial was terminated prematurely, after enrolling only 50 of 380 planned patients, because BMS terminated its satraplatin development program.

HRPC patients enrolled in the EORTC trial had pretreatment characteristics similar to those in the SPARC trial. The majority of patients were Caucasian (98% in EORTC *vs*. 88.5% in SPARC), elderly men (median age 71.5 years in EORTC *vs*. 70 years in SPARC), with good performance status (76% WHO 0-1 in EORTC *vs*. 90% ECOG 0-1 in SPARC). Similar proportions of patients in each trial had factors associated with poor prognosis, including elevated alkaline phosphatase (36% with ≥2.5 x ULN in EORTC *vs*. 39% with ≥1.5 x ULN in SPARC) and bone pain, reflected by elevated baseline pain scores (42% using analgesics daily in EORTC *vs*. 35% with PPI score 2-5 in SPARC).

The EORTC trial was designed to compare the two treatment arms in terms of survival and time-to-pain progression as primary endpoints. When the sponsor decided to terminate the trial prematurely, a decision was made not to carry forward assessment of PPI scores, so analyses including pain assessments could not be performed. Analyses of PFS [PFS defined as pain progression, worsening of performance status, PSA progression, and death for any cause], OS, and PSA response were performed when all patients had completed trial treatment, with median follow-up of 14.5 months. Results from the EORTC trial suggested significant treatment benefits for satraplatin of similar magnitude to those observed in the SPARC trial (Table 19).

Table 19 Comparison of Common Endpoints in SPARC and EORTC Trials (ITT Populations)

Trial Population	**SPARC Trial: Advanced HRPC previously treated with chemotherapy**			**EORTC Trial: Advanced HRPC not previously treated with chemotherapy**		
Endpoint	**satraplatin/ prednisone (N=635)**	**placebo/ prednisone (N=315)**	**p-value**	**satraplatin/ prednisone (N=27)**	**prednisone alone (N=23)**	**p-value**
PFS						
Median (or Mean*)	24.9 (1.2) wks *	16.2 (1.2) wks *	<0.001	5.2 mo	2.5 mo	0.0228
PFS events, n/N (%)	528/635 (83.1%)	274/315 (87.0%)		25/27 (92.6%)	23/23 (100%)	
HR (95% CI)	**0.67 (0.57-0.77)**			**0.50 (0.28-0.92)**		
Overall Survival						
Median (95% CI)	61.3 wks	57.3 wks		14.9 mo	11.9 mo	0.5788
Deaths, n/N (%)	309/635 (48.7%)	154/315 (48.9%)		23/27 (85.2%)	19/23 (82.6%)	
HR (95% CI)	**0.90 (0.74-1.09)**		**0.296**[a]	**0.84 (0.46-1.55)**		
PSA Response						
CR+PR, n/N (%)	121/476 (25.4%)	28/225 (12.4%)	<0.001	9/27 (33.3%)	2/23 (8.7%)	0.0458[b]

HR: Hazard ratio, CI: confidence intervals
[a] Cox Proportional Hazards model
[b] Fisher's Exact test

7.2 Supportive Safety Information

Since the initiation of satraplatin clinical development in 1992 through the analysis cut-off date of 15 November 2006, a total of 1261 patients received satraplatin in 29 completed (or prematurely terminated) clinical trials. All of these trials were sponsored and conducted by Bristol-Myers Squibb, except for trials GPC SAT3-03-01, SAT1-04-01, SAT1-04-03 and SAT1-04-04 which were conducted by GPC Biotech. These trials include:

- 9 clinical dose-finding/pharmacokinetic (PK) trials: 6 dose-finding trials, 1 food-effect trial *[SAT1-04-01]* and 2 trials to explore the effects of varying degrees of renal *[SAT1-04-03]* and hepatic *[SAT1-04-04]* impairment on satraplatin PK (ongoing);
- 5 trials in HRPC: the phase III SPARC trial *[GPC SAT3-03-01]* in patients with advanced HRPC previously treated with chemotherapy, the prematurely terminated phase III EORTC trial *[CA142-025]* in patients with advanced HRPC not previously exposed to chemotherapy and 3 small exploratory trials *[CA142-013, CA142-026 and CA142-029]*;
- 15 other clinical trials (5 combination phase I trials, 7 phase II monotherapy trials in other cancer indications (ovarian cancer, breast cancer, cervical cancer, colon cancer, non-small cell lung cancer and small cell lung cancer) and 3 phase I/II trials of satraplatin in combination with radiotherapy for treatment of patients with lung and head and neck cancers).

To provide additional information to the SPARC trial in a similar indication and patient population, data in 56 patients who received satraplatin for advanced HRPC in 3 small exploratory trials *[CA142-013, CA142-026 and CA142-029]*, were integrated into a Prostate Pool. The EORTC trial *[CA142-025],* that included 27 patients who received satraplatin, was considered separately because safety data were not collected in the same manner as in the SPARC and other HRPC trials (i.e., only the highest grade toxicity reported over all cycles was reported and adverse event onset and resolution dates were not collected).

With the exception of the HRPC trials and 3 recent PK trials examining the effects of food *[SAT1-04-01]*, renal impairment *[SAT1-04-03]* and hepatic impairment *[SAT1-04-04]*, there were no source data or CRFs available.

Information most relevant to the indication for the treatment of patients with HRPC after failure of prior chemotherapy and the dosage recommended (80mg/m^2 orally daily for 5 consecutive days in courses repeated every 5 weeks) comes from the SPARC trial.

7.2.1 Extent of Exposure

The median total exposure to satraplatin was lower in the SPARC trial (2600 mg) than in the EORTC trial (3150 mg), consistent with the lower dose level selected for the SPARC trial (Table 20). The total exposure to satraplatin in the food effect trial was similar to the SPARC trial, consistent with the same regimen and similar median number of cycles. The total exposure to satraplatin in the renal and hepatic impairment trials was about half that of the SPARC trial, consistent with the same regimen but half the median number of cycles administered.

Table 20 Overall Extent of Exposure to Satraplatin

Trial type	Number of Patients	Satraplatin Regimen	Median (range) Cycles	Median (range) Total Dose (mg)
Advanced HRPC				
SPARC Trial	629	80 mg/m^2 dx5 q35d	4 (1-28)	2600 (260-29000)
EORTC Trial	27	100 mg/m^2 dx5 q35d	4 (1-15)	3150 (900-15250)
Prostate Pool[a]	56	80-120 mg/m^2 dx5 q28-35d[a]	2.5 (1-16)	2625[a]
	712			
Recent pharmacokinetic studies				
SAT-1-04-01	17	80 mg/m^2 dx5 q35d	3.5 (1-10)	2625[b]
SAT-1-04-03	24	80 mg/m^2 dx5 q35d	1.9 (1-6)	1425[b]
SAT-1-04-04	19	80 mg/m^2 dx5 q35d	1.9 (1-4)	1425[b]
	60			

a: Prostate Pool includes trials CA142-013 (n=39), CA142-026 (n=10), and CA142-029 (n=7). All but 4 of 56 patients in the Prostate Pool received satraplatin doses >80 mg/m^2. The total exposure is calculated based on a median dose of 210mg (range: 50-320) and median of 3.5 cycles (range: 1-16), i.e., 210mg x 5 x 2.5 = 2625 mg.

b: Estimated assuming a median dose of 150 mg (i.e., 80 mg/m^2 x 1.9 m^2) x 5 doses/cycle x number of cycles. Body surface area was estimated from median weight and height in each trial.

7.2.2 Treatment-Emergent Hematologic Events

A comparison of hematologic abnormalities reported in the SPARC trial with those reported in the EORTC trial and Prostate Pool is provided in Table 21. Although the SPARC trial used NCI CTC v.2 criteria for grading toxicities, all the other studies used NCI CTC v.1 criteria. Results support the conclusion that satraplatin treatment is associated with myelosuppression.

Table 21 Hematologic Abnormalities in the Satraplatin Arm in Studies in Advanced HRPC

Variable	Number (%) of Patients					
	All Grades			Grade 3-4		
	SPARC (N=629)	EORTC (N=27)	Prostate Pool (N=56)	SPARC (N=629)	EORTC (N=27)	Prostate Pool (N=56)
Hemoglobin	603 (95.9%)	26 (96.3%)	56 (100.0%)	59 (9.4%)	0	11 (19.6%)
Platelets	549 (87.3%)	27 (100.0%)	55 (98.2%)	133 (21.1%)	8 (29.6%)	28 (50.0%)
Leukocytes	478 (76.0%)	18 (66.7%)	*	86 (13.7%)	7 (25.9%)	*
Neutrophils	419 (66.6%)	6 (22.2%)	*	133 (21.1%)	4 (14.8%)	*

* Results reported for ≤25% of patients

7.2.3 Treatment-Emergent Non-Hematologic Events

A comparison of the incidences of non-hematologic abnormalities reported in the SPARC trial with those reported in the EORTC trial and Prostate Pool shows a higher incidence of TEAEs for the Prostate Pool compared with the SPARC trial for Grades 3-4 (Table 22). Since all but 4 patients in the Prostate Pool received doses of 100-120 mg/m^2 and patients in the EORTC trial received 100 mg/m^2 compared to 80 mg/mg^2 in the SPARC trial, these results suggest that the incidence and severity of non-hematologic events increases with increasing dose intensity.

Table 22 Non-Hematologic Toxicities in HRPC Studies with Significantly Higher Incidence in Satraplatin compared to Placebo Group in the SPARC Trial

	Number (%) of Patients[A] with Grade 3-4 Adverse Events		
MedDRA System, Preferred Term	**SPARC (N=629)**	**EORTC[C] (N=27)**	**Prostate Pool[B] (N=56)**
Gastrointestinal	49 (7.8%)		21 (37.5%)
Constipation	13 (2.1%)	0	1 (1.8%)
Diarrhea	13 (2.1%)	2 (7.4%)	12 (21.4%)
Nausea	8 (1.3%)	0	7 (12.5%)
Vomiting	10 (1.6%)	2 (7.4%)	7 (12.5%)
General	48 (7.6%)		11 (19.6%)
Asthenia	21 (3.3%)		1 (1.8%)
Fatigue	11 (1.7%)	0	4 (7.1%)
Infections	25 (4.0%)	2 (7.4%)	1 (1.8%)
Metabolism	24 (3.8%)		7 (12.5%)
Nervous	20 (3.2%)		3 (5.4%)
Respiratory	19 (3.0%)	0	5 (8.9%)
Cough	0		0
Dyspnea	6 (1.0%)		3 (5.4%)
Vascular	15 (2.4%)		6 (10.7%)
Deep vein thrombosis	4 (0.6%)	0	2 (3.6%)

[A] Multiple reports of the same preferred term for a patient were counted only once within each treatment group
[B] Prostate Pool includes Studies CA142-013 (n=39), CA142-026 (n=10), and CA142-029 (n=7). All but 4 of 56 patients in the Prostate Pool received doses >80 mg/m^2.
[C] AE reporting in the EORTC trial was limited to minimal reporting of the most severe events.

7.2.4 Intrinsic Factors

Hepatic Impairment

Nineteen patients with refractory solid tumors were entered in the ongoing Phase I trial to assess the effects of hepatic impairment on the pharmacokinetics of satraplatin following oral administration of 80 mg/m^2 for 5 consecutive days, repeated every 35 days *[SAT1-04-04]*. As of 3 January 2007, all patients experienced at least 1 TEAE on trial. The AEs were qualitatively similar to those experienced in the SPARC trial. Only 26% of patients experienced myelosuppression, including neutropenia (16%) and thrombocytopenia (11%).

Renal Impairment

Twenty-four patients with refractory solid tumors were entered in the ongoing Phase I trial to assess the effects of renal impairment on the pharmacokinetics of satraplatin following oral administration of 80 mg/m^2 for 5 consecutive days, repeated every 35 days *[SAT1-04-03]*. As of 3 January 2007, 96% (23/24) of patients experienced at least 1 TEAE on trial. The AEs were qualitatively similar to those experienced in the SPARC trial. Only 33% (8/24) of patients experienced myelosuppression, including thrombocytopenia (17%), leukopenia (13%), anemia (13%), and neutropenia (8%).

7.2.5 Extrinsic Factors

In the Phase I trial to determine satraplatin pharmacokinetics under fasted and fed conditions following administration of 80 mg/m^2/day for 5 consecutive days, with cycles repeated every 35 days, to patients with refractory solid tumors *[SAT4-04-01]*, all 17 patients who completed pharmacokinetic assessments over 2 cycles of treatment reported at least 1 TEAE on trial *[SAT1-04-01]*. Overall, the reported TEAEs were similar to those experienced in the SPARC trial.

8. BENEFITS AND RISKS CONCLUSIONS

The results reported from the protocol-specified early analysis of the SPARC trial are being considered for accelerated approval of satraplatin for treatment of patients with HRPC that has progressed after (or failed to respond to) first-line chemotherapy. Overall, results from the SPARC trial show that satraplatin provides a highly statistically significant and clinically relevant treatment benefit across the heterogeneous disease spectrum of HRPC and is well tolerated by an elderly patient population. No other agent been successfully tested in second-line chemotherapy in that disease.

Efficacy

Results from the SPARC trial demonstrate significant benefit, including a highly significant 33% reduction in risk of disease progression or death ($p<0.0001$), 36% delay in time-to-pain progression ($p<0.0001$), and approximately twice the pain response rate and PSA response rate, with a correlation between the two indicating that the effect of satraplatin on pain results from an antitumor effect. Importantly, treatment benefits of similar magnitude on the primary PFS endpoint were observed regardless of the type of progression event (radiographic or pain); type of prior therapy (docetaxel or other); baseline characteristics such as presence or absence of disease-related pain, performance status, and laboratory parameters; and geographic region (North America, Europe, South America). These findings support the conclusion that satraplatin's utility extends across the highly heterogeneous disease spectrum.

The SPARC trial meets all the criteria outlined in the FDA Guidance for Industry *"Providing Clinical Evidence of Human Drug and Biological Products"* for an effectiveness claim based on a single pivotal trial:

- Large multicenter trial
  The SPARC trial was a large, multinational, multicenter trial, involving 950 patients from 170 sites across 16 countries. The 11 largest accruing sites accounted for 24.3% of total patients, but each of these sites contributed only 1.9% to 2.9% of total patients. Consequently, no single site provided an unusually large fraction of patients and no single investigator or site could have been disproportionately responsible for the favorable effect observed.
- Consistency across trial subsets
  The SPARC trial was designed to have relatively broad eligibility criteria to encompass the range of patients representative of what is acknowledged to be a highly heterogeneous disease. Treatment benefits of similar magnitude were obtained for both PFS and time-to-pain progression for all pre-specified subsets of clinical and prognostic relevance, including type of prior chemotherapy (docetaxel or other), disease-related pain (PPI score 0 or 1-5), bisphosphonate use (yes or no), performance status (ECOG 0-1 or 2), type of progression after initial chemotherapy (radiographic progression or PSA increase only), LDH level (<2 x ULN or ≥ 2 x ULN), hemoglobin level (>11.0 g/dL or ≤ 11.0 g/dL), alkaline phosphatase level (<1.5 x ULN or ≥ 1.5 x ULN), and geographic region (North America or other). The consistency across trial subsets supports the conclusion that satraplatin's utility was not limited to a particular subgroup.

- Multiple endpoints involving different events
  Multiple endpoints were analyzed including PFS, time-to-pain progression and overall survival (interim analysis); as well as pain response, objective tumor response (RECIST criteria), and PSA response. Moreover, PFS was a composite endpoint that included progression events based on radiographic progression, skeletal events, and symptomatic progression, including pain progression, weight loss, and worsening performance status. Consistent treatment benefits of similar magnitude, favoring satraplatin, were observed for the ITT population in terms of time to tumor progression or death and time-to-pain progression or death which, together, accounted for more than 80% of the progression events. The consistency of treatment benefit, particularly for the different components of the composite progression endpoint, greatly reduces the possibility that the positive findings were a chance occurrence.
- Statistically very persuasive finding
  In this large, multicenter trial, the finding of $p<0.0001$ for the primary endpoint of PFS and secondary endpoint of time-to-pain progression is inconsistent with the null hypothesis of no treatment effect.

Additionally, the SPARC trial was both well designed and well executed. During the course of the trial, an independent Data Monitoring Board (DMB) periodically reviewed the conduct of the trial for compliance with protocol and applicable safety standards and confirmed in writing that the Sponsor's conduct of the trial was appropriate, safe, and acceptable. Prior to release of unblinded data to the Sponsor on 15 September 2006, the independent DMB accepted and reviewed a full copy of the unblinded tables and figures summarizing the safety and efficacy findings of the trial at the time of final analysis of PFS. Following their review, the DMB confirmed that the SPARC trial had met the statistical thresholds established for the interim and final analyses of PFS and recommended release of the unblinded data to the Sponsor. The DMB also recommended that the Sponsor take all necessary steps to secure the integrity of the final OS analysis that is scheduled to occur after 700 death events have been observed.

The SPARC trial employed central, blinded reviews of key data to avoid ascertainment bias. Patient pain and analgesic diaries were reviewed and scored independently by two blinded reviewers, with any discrepancies between reviewers mediated by the Medical Monitor. Radiographic images from all 950 patients were reviewed by two blinded radiologists, with any discrepancies between reviewers mediated by a third blinded radiologist. Results from the diaries reviews, radiographic reviews, and clinical events were reviewed independently by blinded medical oncologists, who adjudicated all progression events; these reviewers had no access to investigator assessments, blood counts, and (except for the first 53 cases) PSA values.

The SPARC trial also was well executed in terms of balance between the two treatment arms in term of baseline demographics and characteristics; dosing compliance; patient disposition and reasons for discontinuation; completion of scheduled and unscheduled assessments; completeness of records for critical assessments of disease progression; and the type and proportion of patients receiving follow-on chemotherapy after progression on the SPARC trial. Per protocol, crossover of patients from placebo to satraplatin was not permitted following disease progression and no waivers allowing such crossover were granted.

Safety

Overall, satraplatin was well tolerated in this elderly patient population. The overall level of drug compliance in the two treatment arms (≥94% of planned dose intensity) provides additional support for the safety and tolerability of oral satraplatin.

Myelosuppression is the most frequent toxicity observed with satraplatin therapy, with Grade 3-4 thrombocytopenia in 21.8%, Grade 3-4 neutropenia in 21.1% of patients, and Grade 3-4 febrile neutropenia in 0.3% of patients. However, Grade 4 neutropenia (4.1% of patients), leukopenia (1.0%), anemia (1.7%), and thrombocytopenia (0.3%) were uncommon and Grade 3-4 febrile neutropenia was rare (0.3%).

Complications of myelosuppression included bleeding/bruising, infections, and transfusions. Bleeding/bruising was more frequent among patients in the satraplatin arm than in the placebo arm (9.7% *vs.* 4.5% of patients, p=0.005), but there was no difference between treatment arms in terms of Grade 3-4 manifestations. The rate was significantly higher in the satraplatin arm compared to the placebo arm (p<0.001) for both red blood cell transfusions (16.2% *vs.* 8.0% of patients) and platelet transfusions (4.0% *vs*. 0.3% of patients).

The majority of non-hematologic TEAEs were Grade 1-2 reactions. Among clinically significant non-hematologic toxicities, Grade 3-4 diarrhea (1.9%), vomiting (1.6%), infectious episodes (pooled, 4.5%), and thrombosis (pooled, 1.7%) were also uncommon, but statistically more frequent in the satraplatin arm.

Determining the causality of these adverse reactions was made difficult in the SPARC trial by the concomitant use of granisetron and the much longer exposure to prednisone in the satraplatin arm. Granisetron is known to produce fatigue, asthenia, constipation and QTc prolongations. Chronic use of prednisone is known to produce muscle weakness, infections and gastrointestinal manifestations, including hemorrhage. Also, patients remained on trial for much longer in the satraplatin arm (median of 4 cycles of therapy) than in the placebo arm (median of 2 cycles of therapy).

On-study deaths in the SPARC trial (i.e. deaths within 30 days after the last dose of trial drug or resulting from a TEAE) occurred at about the same rate in both the satraplatin (4.1%) and placebo (4.5%) arms and due to the same causes, primarily disease progression (69% *vs*. 57% of patients in the satraplatin and placebo arms, respectively).

Overall, given that satraplatin is a chemotherapeutic agent, it has demonstrated a favorable safety profile.

Conclusion

Efficacy and safety data from the SPARC trial provide preliminary evidence prior to formal demonstration of patient benefit in HRPC that has failed prior chemotherapy, a life threatening condition, as required under Subpart H to make satraplatin available on the market.

As discussed above, the target patient population is comprised mostly of elderly men. These patients, having failed first-line chemotherapy, have a relatively short life-expectancy and frequently suffer from painful bone metastases. There currently are no approved drugs that have demonstrated efficacy and safety in this setting.

Satraplatin therapy is associated with disease control and pain control. It offers the flexibility of an oral chemotherapeutic option which currently is not available in that setting.

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