European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR Orplatna

International Nonproprietary Name:
Satraplatin

Procedure No. EMEA/H/C/888

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the Rapporteurs consider that the application for satraplatin (Orplatna®), in second line chemotherapy of Hormone Refractory Prostate Cancer (HRPC), is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of outstanding issues (Section VI).

II. EXECUTIVE SUMMARY

II.1 Problem statement

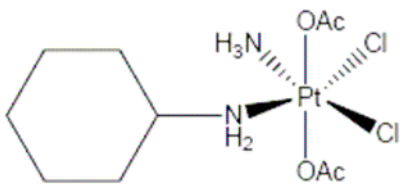
Hormone-Refractory Prostate Cancer (HRPC) is defined as disease progression in the presence of castrate levels of testosterone, along with the lack of response to withdrawal of anti-androgens or other hormonal therapies. Disease progression can be observed by new or worsening metastatic lesions, increasing symptoms related to tumor growth, or sequential elevation in PSA levels. HRPC is generally characterized by pain from bone metastases, a decreasing functional status, fatigue, and eventually bone marrow failure. Once symptoms develop, most patients are significantly disabled by their disease.

HRPC is a disease where patients have limited treatment options available. At present there is no curative systemic treatment for patients with metastatic HRPC. Treatment for patients with metastatic HRPC is primarily palliative and options include:

- Supportive care with corticosteroids (e.g., prednisone and prednisolone), to reduce pain.
- Local radiation, to treat the non-diffuse painful metastases, which occur in about 85% of progressive, hormone-resistant cancers.
- Bisphosphonates, which do not have any antitumor activity.
- Chemotherapy, to slow disease progression, prolong survival and improve QoL, e.g. docetaxel: mitoxantrone, cyclophoisphamide or estramustine are also used
- Systemic radio-isotopic therapy, e.g., strontium
- Other hormonal manipulations, e.g. anti-androgen withdrawal, ketoconazole

II.2 About the product

Orplatna (satraplatin) contains satraplatin, an antineoplastic agent belonging to a new class of octahedral platinum (IV) compounds that are absorbed by the oral route (ATC: L01XA04). The lipophilic properties of these compounds, and hence their absorption, are largely determined by the nature of the axial acetate ligands and the cyclohexylamine group.



Molecular formula: $C_{10}H_{22}Cl_2N_2O_4Pt$
Molecular weight: 500.3

Satraplatin exerts its biological activity via reactive biotransformation products that bind to DNA (to form both inter and intra-strand cross-links) causing the inhibition of DNA replication, cell cycle arrest and induction of apoptosis leading to cytotoxic and antitumor effects. The cytotoxic effect of satraplatin is not cell-cycle specific.

The proposed indication for use, in combination with prednison or prednisolone, is "treatment of patients with metastatic hormone-refractory prostate cancer (HRPC), who have failed prior chemotherapy."

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

Formal scientific advice was given by CHMP (22 January 2004; 28 September 2005; 24 February 2006) and scientific recommendation was given by Agence Francaise De Securite Sanitaire des Produits de Sante (AFSSAPS, France, 25/11/2003 and 6/11/2006), Bundesinsitut fur Arzneimittel und Medizinprodukte, (BfArM, Germany, 16/09/2003 and 16/10/2006), Medicine Evaluation Board (MEB, The Netherlands, 02/10/2003), Medicines Products Agency (MPA, Sweden, 01/10/2003 and 11/10/2006), Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom, 01/08/2003), Agencia Espanola del Medicamento y Productos Sanitarios (AEMPS, Spain, 23/11/2006), Danish Medicines Agency (DMA, Denmark, 10/11/2006).

Satraplatin (JM-216) is a novel, orally absorbed, platinum (IV) complex. It was the product of a collaborative development program between Bristol-Myers Squibb (BMS), Johnson Matthey (JM) and the Institute of Cancer Research (ICR) with the aim of developing an orally active platinum drug possessing at least comparable antitumor activity to and no cross-resistance relative to cisplatin, but with a toxicological profile similar to or better than that of carboplatin. Following the termination of development by BMS, satraplatin was licensed by JM to Spectrum Pharmaceuticals in January 2002 and sublicensed to GPC Biotech in October 2002. Pharmion obtained the rights to satraplatin in the European Union in December 2005.

The clinical development plan that establishes the foundation for this submission of satraplatin for 2nd line treatment of HRPC is based on one pivotal study GPC SAT3-03-01 (to be further designated as SPARC study) conducted in 950 HRPC patients. The design of this study has been revised based on comments by the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice Working Party (SAWP), and the Office of Oncology Drug Products (Center for Drug Evaluation and Research [CDER], Food and Drug Administration [FDA]). The Applicant states that the study has been executed in compliance with Good Clinical Practices and according to all relevant international, national, and local regulations.

II.4 General comments on compliance with GMP, GLP, GCP

Inspections of the drug substance manufacturing site and/or the drug product manufacturing site and/or the batch release site are not considered necessary.

Pivotal toxicology studies and safety pharmacology studies were performed under GLP.

The Applicant indicated that all studies in the satraplatin clinical development program were performed in concordance with current standards for the design, conduct, and analysis of clinical research, including ICH GCP and all region-specific requirements.

II.5 Type of application and other comments on the submitted dossier

The application is a full, stand alone application in accordance with Directive 2001/83/EC Article 8. The Application is made through the CHMP Centralised Procedure with Dr. van Zwieten-Boot (NL) acting as Rapporteur and Dr. Demolis (FR) as Co-Rapporteur. The application concerns Orplatna, hard capsules, which contain the active substance satraplatin.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

The product at issue is a hard capsule with the new drug substance satraplatin. Two strengths are proposed: 10 mg and 50 mg. The product is indicated for the treatment of patients with metastatic hormone-refractory prostate cancer, in combination with prednisone or prednisolone, who have failed prior chemotherapy. The maximum daily dose is 80 mg/m^2, taken orally. For an adult person of 1.8 m^2 this would be 140 mg. The capsules are packaged in PVC/Aclar® blisters and heat sealed with a push-through foil backing. Each blister contains five capsules. The blisters are sealed in an opaque paperboard wallet card. Each wallet card is folded such that the outer appearance is that of a carton for distribution.

III.1 Quality aspects

Introduction

The product at issue is a hard capsule with the new drug substance satraplatin. Two strengths are proposed: 10 mg and 50 mg. The product is indicated for the treatment of patients with metastatic hormone-refractory prostate cancer, in combination with prednisone or prednisolone, who have failed prior chemotherapy. The maximum daily dose is 80 mg/m^2, taken orally. For an adult person of 1.8 m^2 this would be 140 mg. The capsules are packaged in dark amber PVC/Aclar® blisters and heat sealed with a push-through foil backing. Each blister contains five capsules. The blisters are sealed in an opaque paperboard wallet card. Each wallet card is folded such that the outer appearance is that of a carton for distribution.

Drug Substance

Satraplatin is neither described in the Ph.Eur. nor in a Pharmacopoeia of one of the EU member states. The ASMF-procedure is used. Satraplatin is an off-white to pale-yellow, non-hygroscopic powder. Scanning electron microscopy indicate irregular-shaped crystalline plates. No evidence of additional polymorphs was found. The substance is very slightly soluble in water. Aqueous solubility is 0.3 mg/ml at 23°C at pH 5.0, which remains practically the same at pH 1.4 and pH 7.4.

- Manufacture

A flow diagram is present of the complete manufacturing process. The synthetic route has remained essentially unchanged throughout the clinical development of satraplatin. Appropriate specifications have been adopted for the solvents and reagents. This key starting materials have been adequately characterized.

- Quality Control

In the drug substance specification requirements have been adopted for appearance, identification (IR and HPLC), related substances (HPLC), assay (HPLC), water content, metallic impurities, residual solvents, and particle size. The limits for all parameters are in line with toxicology data and relevant guidelines. Satisfactory batch analysis data are available.

- Stability

For three pilot scaled batches and three commercial batches stability data have been submitted. These batches were stored in amber glass bottles at 40ºC/75% RH (6 months) and 30ºC/65% RH (up to 36 months). Parameters tested were appearance, X-ray powder diffraction, water content, impurities, and the assay. The stability data justify a retest period of 3 years, without any special storage temperature. The drug substance should however be stored in the original package in order to be protected from light.

Drug Product

- Pharmaceutical Development

The excipients included in the product are commonly used in oral capsules. All excipients meet the specifications of the Ph.Eur. During early development five different strengths (5, 10, 50, 100, and 200 mg) were developed. The 10 mg and 50 mg strengths were selected for commercial use. The 50 mg strength used in the Phase 1 and Phase 2 trials was identical to the proposed commercial composition. The 10 mg capsules contained larger amounts of excipients. However, the percentages of excipients were comparable (microcrystalline[efm1] cellulose and lactose versus and for the commercial product) or identical (sodium starch glycolate and magnesium stearate). All Phase 3 batches had the proposed commercial composition were produced by the commercial process at the commercial site.
The manufacturing process has undergone only minor modifications during development and clinical trials. For all clinical trial formulations dissolution data have been provided which show that the differences in formulation and manufacture do not influence dissolution. The development and discriminatory power of the dissolution method has been described and adequately discussed by the applicant.
Early pre-clinical testing using microcrystalline satraplatin which had a narrow particle size range, concluded that oral efficacy was not improved when compared to the material formulated without particle size reduction. Nonetheless, a requirement has been set to assure consistency of manufacturing and product performance.

- Manufacture

A conventional and standard manufacturing process is applied. The capsule fill weight is a critical parameter and is monitored periodically throughout encapsulation. In general the description of the process and the in-process controls are adequate. Bulk capsules have been demonstrated to be stable during up to 12 months storage at 30°C/65% RH in bulk LDPE bags.
Blending is identified as the most critical step in view of homogeneity. Different blending times were therefore tested in order to assure consistent drug content throughout the blend. In view of the data on homogeneity and taking into account in-process controls, it is considered acceptable to perform a formal validation post approval. A process validation scheme is provided in section 3.2.R.2 of the dossier: three common blend batches at the commercial scale will be manufactured according to the approved process validation protocol. The protocol is acceptable.

- Quality Control

In the drug product specification requirements have been adopted for appearance, identification (HPLC), related substances (HPLC), assay (HPLC), water content, dissolution, and uniformity of dosage units. In view of batch analysis data and stability results, the limits for all specified impurities and total impurities are acceptable. Satisfactory batch analysis data of pilot scaled and one commercial sized drug product batch are available.

- Stability

Stability data are presented for up to 36 months storage in blister packaging. The attributes of appearance, assay, related substances, dissolution, water, and microbial purity have been tested. The pilot scaled batches were stored during up to 24 months at 30°C/65% RH and 6 months at 40°C/75% RH. Stability studies with commercial scaled batches will be started in due course. In view of the stability data the proposed shelf-life of 48 months can be granted. The additional storage condition is 'Keep the blister in the outer carton in order to protect from light'.

Conclusion:
From a chemical-pharmaceutical point of view all issues are solved and no objections are present against a marketing authorization.

III.2 Non clinical aspects

Pharmacology
Satraplatin is a cytotoxic agent. Satraplatin treatment results in platinum DNA-adduct forming, slowing down of the S phase, resulting in G2 block and subsequent cell death. In addition satraplatin and its metabolite JM-118 were potent irreversible inhibitors of purified and intracellular Trx reductase (TrxR), thus sensitizing the cell for DNA damage. The Applicant considers that inhibition of TrxR and angiogenesis represent novel aspects of the mechanisms of action of satraplatin and JM-118. However, a specific anti-angiogenic effect was not proven, and data on TxR are not available for other platinum-based drugs.
The cytotoxic activity of satraplatin has been shown *in vitro* against various tumour cell lines, including three prostate carcinoma cell lines. The observed cytotoxicity was comparable with other platinum analogues. In addition also some cisplatin resistant tumour cell lines were sensitive to satraplatin treatment *in vitro*. This may be due to an altered mechanism of cellular uptake (satraplatin by passive diffusion instead of active transport for e.g. cisplatin).
No cross-resistance to satraplatin or its metabolite JM-118 has been found in cells resistant to taxanes, doxorubicin, vincristine, etoposide, mitoxantrone, and camptothecin. Acquired resistance to satraplatin *in vitro* could be attributed to either increased levels of GSH, increased DNA repair or intracellular sequestration.
Satraplatin had no/limited effect on PSA transcription, suggesting that PSA levels are not directly influenced by satraplatin treatment and indicating that PSA may still be used as a marker for tumour progression in the clinic.
Antitumour activity of Satraplatin was studied in one human prostate carcinoma model *in vivo*. In this model using the PC-3 cell line satraplatin effectively reduced tumour growth. Several other *in vivo* prostate tumour models have been described in literature; but these were not used by the Applicant. As supportive data *in vivo* studies (human tumour xenograft or mouse syngeic tumour models) using other tumour types

were presented. In all except one antitumour activity of satraplatin was clearly evident. In general no regression or remission was seen, only reduced tumour outgrowth was observed.
No therapeutic effect of satraplatin treatment was observed in the only *in vivo* study with a transplanted cisplatin-resistant tumour.
The schedule dependency was only tested in one study. In this study, a daily x5 schedule was superior to single dose or continuous dosing. The schedule dependency was not investigated in human prostate carcinoma models.
No secondary pharmacodynamic studies were performed, which is accepted.
In the safety pharmacology studies no acute side effects were observed *in vitro* and *in vivo* and after a single dose of satraplatin. All viral organ systems were addressed (CNS, the cardiovascular system, the, respiratory system, renal system and the GI tract).
Synergistic effects co-treatment of satraplatin with paclitaxel and docetaxel was seen *in vitro* and *in vivo*. Also a potentiating effect of satraplatin on radiation was observed *in vivo*. For etoposide synergy of satraplatin was seen in only one of two mouse models.
The co-incubation with prednisolone had only a marginal effect on the cytotocic activity of satraplatin to prostate tumour cells *in vitro*.

Pharmacokinetics
The pharmacokinetics of clinically used platinum compounds (e.g., carboplatin, cisplatin and oxaliplatin) have been characterised by measurement of total platinum in plasma and plasma ultra-filtrate (PUF). Similarly, for satraplatin, validated analytical methods were used to characterise the disposition of total platinum in plasma, PUF and other biological matrices. The methods employed for measurement of platinum after administration of satraplatin were Atomic Absorption Spectrophotometry (AAS) and Inductively Coupled Plasma-Mass Spectrophotometry (ICP/MS). A specific assay for satraplatin and three biotransformation products (JM-118, JM-383 and JM-518) in PUF using liquid chromatography with mass spectrometric detection (LC-MS/MS) was developed. A Liquid Chromatography with Inductively Coupled Plasma-Mass Spectrophotometry (LC-ICP/MS) method was developed to generate chromatographic "fingerprints" of platinum-containing moieties after oral administration of satraplatin to the rat, dog and human. The developed analytical methods were validated sufficiently. No validated analysis methods were developed for mouse and monkey.
Satraplatin appeared to be unstable in blood at 37ºC. In order to decrease the extent of *ex vivo* metabolism, blood samples were placed on wet ice, kept cold during processing and plasma separated from whole blood as soon as possible after collection. As observed with other platinum formulations, the percentage protein bound satraplatin was high and increased over time after either oral or intravenous administration in the rat and dog. Therefore, the concentration of platinum in PUF (i.e., free platinum) was used for the characterisation of safety and efficacy as well as for interspecies comparisons.
Pivotal non-clinical pharmacokinetic studies were performed in Sprague Dawley CD rats and Beagle dogs, which were also the primary toxicology species.
Bioavailability of satraplatin was low in the investigated species: ~15% in rat, 30-40% in dog and 8.5% in monkey. The decrease in bioavailability with increasing dose was attributed to the low aqueous solubility of satraplatin (~300 µg/ml).
In the mouse, dose-related increases were observed in platinum exposure in PUF up to satraplatin doses of 200 mg/kg after a single oral dose and no accumulation was noted after 44 days of daily dosing. Dosage regimen for repeated dose studies in the rat and dog were designed to simulate those utilised in human clinical studies, i.e., one or more cycles of five days of daily oral dosing followed by an off-dose period of 3-4 weeks between cycles. In rats and dogs, after repeated oral doses of satraplatin, the platinum exposure in PUF increased in a dose-related, but not dose-proportional manner up to 40 mg/kg and 13.5 mg/kg, respectively. This less than dose proportional increase in exposure could be due to saturated absorption in the gastro-intestinal tract or the low solubility of the product. Furthermore, gender differences in AUC were observed in rat (female > male), but not in dog. This could be due to gender differences in CYP in female and male rats.
In a pharmacokinetic study performed in dogs after a single dose, or five days of oral dosing with a capsule or by gavage; concentrations following gavage were almost twice those following capsule. Despite these results, administration by capsule has been chosen for toxicology studies for practical reasons. Exposure was used as a marker rather than dose.
In mouse, the terminal elimination half-life of platinum ranged from 29.5 to 31.6 h in plasma and 1.5 to 2.3 h in PUF. These results indicate that the half life of unbound drug is much shorter than that of bound drug

in mouse. However, in rat the half-life of platinum after the fifth oral once-daily dose was 96 h in plasma and 147 h in PUF. This apparent long half-life in PUF after repeated administration might be attributed to saturation of the irreversible plasma protein binding. In humans, the half life was 100 h in plasma and 32 h in PUF. No half life and clearance data were provided for dog plasma and PUF. Based on the provided plasma and PUF versus time curves, half life is expected to be considerable longer than in mouse (longer in plasma than in PUF).
Accumulation factors for platinum in PUF, within a five-day dosing cycle, ranged from one (no accumulation) to approximately 1.6. Approximately 20-30% of the total platinum present in rat and dog PUF could be accounted for by JM 118, the only satraplatin metabolite with concentrations above the LOQ. Concentrations of JM-383 in rat and dog after oral administration were below the LOQ. In humans, no unchanged satraplatin or JM-383 was measured in PUF after oral administration of 2.1 mg/kg (80 mg/m2). JM-118 accounted for 15-47% of the total platinum in PUF. The identities of the remaining platinum-containing moieties have not yet been elucidated.
Tissue distribution studies were conducted using radio-labelled satraplatin in the mouse and by measurement of platinum in tissues in the mouse, dog and monkey. In the rat, platinum was present in most tissues at high concentrations after oral administration of a single dose and after five days of once daily dosing of 15 mg/kg of satraplatin. Levels of platinum two hours after the fifth daily oral dose were greater than 1 µg/g tissue in prostate, bone marrow, kidney, lymph nodes, liver, lung, ovaries and spleen; plasma and PUF platinum concentrations were approximately 0.8 and 0.05 µg/ml, respectively. The elimination half-life of platinum from tissues after five days of daily oral dosing was long, i.e., six days or longer. There was generally a 2- to 5-fold accumulation of platinum in tissues. However, this accumulation was not observed for the prostate (target organ) which showed a higher accumulation after 2 h of the first dose compared to other tissues. In rat, the elimination half-life of platinum from tissues after 5 days of oral dosing generally exceeded six days. Exceptions were bone marrow (77 h), large intestine wall (66 h) and thymus (87 h). No marked gender differences with respect to the tissue distribution were observed in this study either after a single dose or after five days of dosing. Platinum concentrations were higher in kidney than in liver in rat, dog and monkey.
The metabolism of satraplatin and the formation of JM-118 from satraplatin are catalysed by human haem proteins in red blood cells, CYP oxidoreductase and possibly multiple CYPs including 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 and other NADPH-dependent reducing enzymes. JM-118 is not metabolised by human CYP oxidoreductase. It has been shown in mouse and dog that the cyclohexyl group is cleaved from satraplatin. The metabolic processes responsible for the cleavage have not been determined, nor have the metabolites resulting from the loss of the cyclohexyl group been identified.
In vitro differences in metabolism between female and male rat liver microsomes were observed (25% versus 60%). *In vivo* gender differences were observed in AUC of rat. Therefore, metabolism could be the cause for the higher AUC in female rat compared to male. Using “metabolic fingerprinting” it was shown that metabolite and/or degradation peaks in human plasma were present in both the rat and/or dog. The rat was a good toxicological model. However, the specific metabolite profile was different in dog compared to rat and human. A large part of the metabolism of satraplatin is unknown. The applicant states that they will continue to work in order to elucidate further the metabolic fate of satraplatin.
Because of the ubiquitous nature of haem proteins, it is very unlikely that co administered drugs could inhibit haem proteins to a sufficient extent to result in a metabolic interaction. Similarly, other drugs are unlikely to affect the clearance of platinum, since platinum, after the oral administration of satraplatin, is primarily cleared by renal elimination Satraplatin is a non-specific inhibitor of multiple CYPs *in vitro* suggesting there may be the potential for satraplatin to cause metabolic interactions with drugs eliminated primarily via metabolism by CYPs. JM-118 was found not to inhibit CYPs. JM-383 showed inhibition versus CYP2C8, 2C9 and 2C19. Satraplatin did not induce any of the CYP isozymes tested, therefore, clinical drug interactions through induction of CYP1A2, 3A4, 2B6 or 2C19 by satraplatin are unlikely.
Following intravenous dosing of satraplatin to the mouse, rat and dog, platinum was primarily excreted in the urine. In dogs, the cyclohexyl group was removed from satraplatin and was excreted in the urine. There was a significantly higher recovery of platinum in faeces after oral dosing; however, the increase in faecal recovery after oral dosing is primarily attributable to the excretion of unabsorbed drug. The results of balance studies of the radioactivity and of the excretion studies of platinum in rat and dog showed large variability, with balance or excretion much lower than 100%. There was a very slow rate of disappearance of platinum from tissues after five days of oral dosing. The long term location of platinum and the time to excrete platinum are not known.

Renal elimination of platinum is also the primary route of elimination for carboplatin, cisplatin and oxaliplatin.

Toxicology

The non-clinical toxicity studies focused on identifying the respective maximum tolerated doses rather than defining a no observed adverse effect level. Pivotal repeat-dose oral toxicity studies have been performed in rats and dogs up to one month of daily dosing. Moreover, studies mimicking the clinical dosage regimen were carried out with satraplatin in rats and dogs up to 7 cycles.

The pattern of toxicity that was similar in all species tested. Non-specific clinical signs (e.g. decreased activity, decrease in body weight gain or body weight loss, piloerection, affected stool and decreased food consumption) usually occurred several days after the start of treatment, and maximal toxicity occurs > 1 week after the last dose. Death occurred several days up to several weeks after treatment, and was preceded by non-specific clinical signs of toxicity. In the single dose studies congestion and haemorrhage contributed to death. In repeated dose studies in rats, bone marrow suppression but also several malignancies (especially in females) contributed to death. In dogs, tonsillar ulceration and necrosis caused by immunosuppression were considered to have contributed to the severe clinical condition of the animals. Effects on lymphoid organs seem to be the primary toxic effect in both rats and dogs, followed by GI lesions. Exposure levels in animals were similar to those measured in the clinic.

At the low doses already effects on haematological parameters was evident (decreased leukocyte, platelet and reticulocyte numbers in peripheral blood) with a nadir at 1-2 weeks after treatment and (almost) complete recovery at the end of the off-dose periods in the 7-cycle chronic toxicity studies. These effects were accompanied by decreased cellularity of marrow and lymphoid organs (severe bone marrow depression), and (in dogs) widespread haemorrhage and an apparent immunosuppression (evident by tonsillar ulcerations and/or bacterial colonisation of the lung).

Satraplatin-induced emesis occurred in dogs at doses of ≥ 1.5 mg/kg in repeat-dose studies, could be reduced by ondansetron a serotonin-5HT3 antagonist. Emesis did not reduce the systemic exposure to satraplatin measured as platinum in PUF. Gastrointestinal effects were seen in several of the repeat-dose studies in rats and dogs. Changes in faeces (mucoid/decreased/liquid/black) were seen in dogs while in both species haemorrhage/congestion/ enlargement was seen at necropsy at intermediate and high dosages. Histopathology revealed apoptosis of mucosal epithelial cells and mucosal erosion. Recovery of the gastrointestinal tract was seen at the end of the recovery periods.

Adverse effects on testes and spermatogenic cells were seen in rats and dogs with little evidence of recovery. Satraplatin was toxic to the male reproductive organs. A reduced number of spermatozoa as well as an increase in degenerate spermatogenic cells in ducts were seen in the epididymides. In addition, seminal vesicles showed atrophy and a reduction in secretion volume. The testes showed seminiferous tubular atrophy.

Renal toxicity was seen in rats (serum electrolyte changes, urine changes, renal tubular degeneration or necrosis), and the histologic changes were still present in the recovery animals. Dogs were less sensitive to renal toxicity, and effects (e.g. electrolyte changes) were observed at lethal doses.

Satraplatin was not hepatotoxic in the current studies.

Platinum analogues have shown to induce neuropathy and ototoxicity in humans. In dogs, no signs of ototoxicity were observed. The only potential signs of neurotoxicity (reluctance to use hind paws) was observed in one dog study at a lethal dose). However CNS effects were not specifically studied in the repeated dose studies. The only potential signs of neurotoxicity (reluctance to use hind paws) was observed in one dog study at a lethal dose. The observed neurotoxic effects of satraplatin appear to be limited when compared to the neurotoxic potential reported in literature for other platinum analogues.

Co-treatment with etoposide did not result in an altered toxicity profile, but reduced the MTD.

Satraplatin is unequivocally genotoxic in the standard 3-test battery. No carcinogenicity studies were performed. However from the 6 month (7 cycles) rat toxicity study it can be concluded that carcinogenic potential of satraplatin is rather strong given the increased incidence in malignancies seen in females (mostly in mammary gland) but also (to a lesser extent) of males.

Only embryo-foetal development studies have been performed. Embryotoxicity was apparent at maternally toxic doses in rats and rabbits. Additionally skeletal developmental variations were seen in rat foetuses only, but also at maternally toxic doses.

Satraplatin had no antigenic potential in an antigenicity study in Guinea Pigs. Despite some differences in metabolic profile between human and dog no additional studies are requested because the differences were

mostly quantitive and because the toxicological profile of satraplatin in dogs and humans is similar (myelosupprression/haematological changes, gastrointestinal toxicity).
The proposed specification limits for impurities JM-2897 (0.4%) and JM-555 (0.2%) are not agreed because these are not qualified in GLP-compliant repeated dose toxicity studies (see question quality section).
In the environmental the PECsurface water has been calculated following refinement of Fpen. Fpen refinement was underpinned by data, and the PEC calculation resulted in a value below the action limit. Based on Log K_{ow} measurement it is concluded that further screening for PBT (persistence, bioaccumulation and toxicity) is not necessary.

Conclusion:
From a non-clinical point of view all issues are solved and no objections are present against a marketing authorization.

III.3 Clinical aspects

Pharmacokinetics
Due to the cytotoxic nature of satraplatin, all pharmacokinetic data were obtained from patient studies. Since irreversibly bound drug is not available to distribute to the site(s) of action, efficacy and safety of satraplatin is expected to be related to the concentration of free platinum (i.e., platinum in PUF), as is the case for e.g. cisplatin and carboplatin.

Absorption
After oral administration of a single 80 mg/m^2 dose of satraplatin to patients with refractory non-hematologic cancers, maximum plasma platinum levels of 225 ± 50 ng/ml were reached after 3.5 hours, and maximum PUF platinum levels of 56.9 ± 19.2 ng/ml after 2.5 hours.
Absolute bioavailability of satraplatin has not been determined in humans, but may well be low, in line with the low absolute bioavailability of satraplatin in mice and dogs (see preclinical assessment). Based on renal excretion data, it is concluded that absorption is at least 5%, and probably not much higher.
A food effect was observed; C_{max} was reduced by approximately 26% upon satraplatin dosing under high fat fed conditions. AUC_{0-24h} was not reduced to a statistically significant extent. Because of these findings, it is proposed by the applicant that satraplatin be administered either 1 hour before or 2 hours after a meal. However, the pharmacokinetic reason to administer satraplatin under fasting conditions is not completely understood. Although peak exposure to unbound platinum is higher when administered under fasting conditions, variability under fasted and fed conditions appear comparable and total exposure is not significantly different. Furthermore, dose reduction from 120 to finally 80 mg/m^2 due to AE was an issue in the clinical development program. Still, administration of satraplatin under fed conditions or irrespective of food is not sufficiently investigated in the pivotal clinical studies, and to expect further studies into this matter at this stage is considered unrealistic. Therefore, although the prerequisite for fasting conditions may complicate the use of satraplatin in clinical practice, the proposed administration without food is accepted.

Distribution
Binding of satraplatin and JM-118 in vitro to plasma proteins was found to be irreversible and increased with time; no reversible protein binding was detected. Binding occurred more rapidly with JM-118 than satraplatin.
Satraplatin binds to plasma proteins. At 0.5 and 8 hours post-dosing, 51% and 89% of platinum was bound to protein. In plasma samples collected 10 hours or later post-dose, approximately 90-94% of platinum was bound to protein. Protein binding of satraplatin was irreversible, similar to that of other platinum drugs, i.e., cisplatin, carboplatin, and oxaliplatin. Since irreversibly bound drug is not available to distribute to the site(s) of action, efficacy and safety is expected to be related to the concentration of free platinum (i.e., platinum in PUF).

Metabolism
The metabolic profile of satraplatin has not been fully elucidated. The only identified platinum (II) metabolite JM-118 accounts for 20-30% of the platinum content in PUF. The formation of JM-118 appears mediated by multiple CYP450s or other NADPH-dependent enzymes. JM-118 was not further metabolized by human CYP450 oxidoreductase. The applicant has not been able to complete the characterisation of the

metabolites formed, due to analytical difficulties. Due to this lack of data on the metabolism pathway of satraplatin, the possible importance of certain genetic polymorphisms in the metabolism of satraplatin is unknown.

Elimination
After absorption, satraplatin appears mainly metabolically cleared, with a terminal half-life of platinum in plasma and PUF being approximately 230 hours. At least part of the formed metabolites are excreted renally. However, it is not possible to make a quantitative prediction of the relative amount of the absorbed dose in humans that is excreted renally, since no mass balance study has been conducted.
Based on preclinical data in mice, rats and dogs, it appears that following iv administration, the majority of the dose is excreted via the urine, and only a small amount, approximately 5% via the faeces (see preclinical assessment). These combined data suggest that renal excretion is important for excretion of satraplatin metabolites from the plasma.

Dose proportionality and time dependency
Platinum exposure appears to increase roughly linear up to a dose of approximately 100 mg/m^2. At higher doses, non-linear pharmacokinetics is observed, most probably due to limited solubility of satraplatin. No solubility problems are expected for the proposed 80 mg/m^2 dose. No unexpected accumulation of plasma and PUF platinum occurs upon multiple once-daily dosing of satraplatin, with an accumulation ratio for plasma platinum and PUF platinum from day 1 to day 5 being 3.0 (95% CI: 2.6-3.5) and 1.5 (95% CI 1.4-1.7), respectively.

Interpatient variability
Interpatient variability at a dose of 80 mg/m^2, the dose utilized in the pivotal SPARC Phase 3 trial, was moderate, with CV values for platinum exposure in PUF of approximately 30% after single and multiple daily dosing. Administration of satraplatin with food did not increase interpatient variability; CV values were comparable whether satraplatin was administered with food or in the fasting state.

Special patient populations

Renal impairment
The clearance of platinum after satraplatin administration appears to be highly dependent on renal function. Patients with mild renal impairment showed comparable exposure and concentrations for both plasma platinum and PUF platinum on day 1 and day 5 of treatment compared with patients with normal renal function. In severe renally impaired patients, plasma and PUF platinum exposure was increased. At day 1 the PUF platinum exposure was approximately 2.5 times higher at day 1, and 3.6-fold increased at day 5. In moderately renally impaired patients, at day 1 the PUF platinum exposure was approximately 1.5 times higher at day 1, and 1.6-fold higher at day 5. The applicant is requested to provide a dose reduction for moderate and severe renally impaired patients. This proposal should be based on the continuous relationship between creatinine clearance and exposure.

Hepatic impairment
A trend toward decreased platinum levels in plasma and PUF was observed as hepatic function decreased, particularly in patients with Child-Pugh Class B and C impairment. No dose adjustment is considered necessary due to apparent pharmacokinetics-related safety concerns. Based on safety arguments, the applicant proposes a dose reduction in severe hepatically impaired patients, i.e., to start with a dose of 60 mg/m^2 instead of 80 mg/m^2.

Gender, race, age
A gender effect is not relevant for the current indication of satraplatin, However, when future indications would result in female being treated with satraplatin, this should then be further investigated by the applicant.
Satraplatin exposure was reasonably comparable in Japanese and non-Japanese patients. No dose adjustment appears necessary at increased weight. However, the lack of a significant effect of weight or body surface on satraplatin pharmacokinetics argues against the use of a BSA-based dose regimen. The applicant should explain the reason for choosing satraplatin dosing per m^2. In clinical practise, BSA-based oral dosing will be impractical.

No dose adjustment is considered necessary based on pharmacokinetics in elderly. Patients up to an age of 87 were included in the study program, and a relatively large number of elderly patients were included in the pharmacokinetic studies. Satraplatin is not expected to be used in children for the current application, and therefore the lack of pharmacokinetic data in children is acceptable.

Interactions
Satraplatin is a non-specific inhibitor of multiple CYP450s (i.e., 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) *in vitro*. However, IC_{50} levels are much higher than levels observed in PUF in vivo after administration of oral satraplatin 80 mg/m^2. Metabolite JM-118 was shown in vitro not to be an inhibitor of CYP450 isoenzymes. *In vitro,* satraplatin does not induce CYP450 1A2, 3A4, 2B6 and 2C19 nor does it inhibit P-gp. Therefore, based on the results obtained from in vitro experiments, no in vivo interaction studies for satraplatin and JM-118 are required. However, other metabolites have not been characterized, nor tested for enzyme inhibiting or inducing properties. When new metabolites have been characterised, the possibility for drug-drug interaction should be considered for these metabolites. Until this is the case, the lack of data should be indicated in the SPC section 4.5.
Very high local exposures, possibly exceeding the µM range IC_{50} for CYP3A4 inhibition, may be possible in the gut. Therefore, the applicant should indicate if CYP3A4 is inhibited by satraplatin, and if orally administered satraplatin will or will not affect bioavailability of other CYP3A4 substrates administered simultaneously by the peroral route. A clinical interaction study with oral midazolam should be conducted in order to investigate this possibility.

For the current application, satraplatin is to be combined with prednisone and prednisolone. In the clinical SPARC study, although not formally investigated, no signs of an interaction are apparent.

A couple of issues are considered unresolved, i.e., with respect to the possible inhibition of CYP3A4 by satraplatin in the gut and the dose advice for renally impaired patients.

Pharmacodynamics
The primary cytotoxic mechanism of satraplatin is similar to that of other platinum compounds including cisplatin, carboplatin and oxaliplatin, and is based on the formation of DNA adducts. Platinum-DNA adducts, which are formed following uptake of the drug into the nucleus of the cell, activate several cellular processes that mediate the cytotoxicity of these drugs. These processes include the signalling of DNA damage, cell cycle checkpoints and arrest, DNA repair and cell death. Platinum compounds as such are not cell-cycle specific, though cells appear to be maximally sensitive to cisplatin in G1, just prior to the onset of DNA synthesis, and minimally sensitive in peak DNA synthesis, with entry into S-phase resulting in a two-fold decrease in sensitivity.
Although satraplatin-derived platinum is known to bind to DNA, actual platinum-DNA adducts nor metabolites that function as precursors for such adducts have not been characterised for satraplatin.

Satraplatin derived platinum irreversibly binds to plasma proteins. Since irreversibly bound drug is not available to distribute to the site(s) of action, efficacy and safety is expected to be related to the concentration of free platinum (i.e., platinum in PUF) instead of total platinum in plasma.

The toxicologic effects of satraplatin are a direct extension of its pharmacodynamic mode of action, i.e., formation of bifunctional adducts with DNA causing distortions in the structure of DNA with subsequent modulation of several signal transduction pathways, cell cycle arrest and cell death due to apoptosis or necrosis
Secondary effects of satraplatin are consistent with its mode of action, i.e., based on the formation of DNA adducts, and consistent with that observed with other platinum-containing medicines. During toxicity studies, satraplatin was found to be mutagenic, embryotoxic, teratogenic, and have tumorigenic effects. These secondary effects are in common with the pharmacologic activity of satraplatin and of other platinum analogues. As the effects of satraplatin are a direct extension of its mode of action as a platinum agent, no secondary pharmacodynamic studies were performed. Conducting secondary pharmacology studies would do little to extend the scientific knowledge of satraplatin that would contribute further to the safe use of satraplatin in humans.
A possibly important difference between satraplatin and other registered platinum medicinal products is that satraplatin is administered orally, in contrast to other registered platinum drugs, which are administered

via IV infusion. Also in light of the apparently low absolute bioavailability of satraplatin, the possibility of local effects, e.g., related to the gastrointestinal tract, caused by satraplatin, may be significant. This is discussed in the safety part of this AR.

In a substudy investigating effects of satraplatin on ECG parameters, no major effects on QT prolongation, requiring further investigations, were observed. Although a number of patients had transient ECG changes, none were considered clinically significant and no corresponding adverse events were reported. No patients experienced QT or QTc intervals of ≥ 500 msec and only 1 patient had a transient increase in QTc of >60 msec. There were no trends in mean QT or QTc changes from baseline and there did not appear to be a relationship between ECG abnormalities and either gender or fed/fasting condition. No trends were observed with respect to QTc changes and time and no relationships were observed between QTc values and platinum concentrations (i.e., plasma platinum C_{max}, plasma platinum C_{24h}, PUF C_{max}, and PUF C_{24h}).

In a population PK-PD study, no significant effect of hepatic impairment status, hematocrit levels, albumin levels, cancer type, or prednisone coadministration on the pharmacokinetics of PUF platinum following oral administration of satraplatin was found.

Relationship between plasma/PUF levels and effect were investigated to a reasonable extent. The maximum tolerated dose (MTD) of satraplatin decreased with increased duration of dosing. After 5 consecutive days of once daily dosing, the MTD ranged from 100-140 mg/m^2/day after 5 days of dosing with DLTs of leukopenia, thrombocytopenia, anemia, and diarrhea.
Based on these data, a dose of 100-120 mg/m^2 was recommended for Phase II studies, applying the once daily x 5 schedule. However, upon applying such dose in subsequent Phase II studies, dose-reductions or delays were necessary on safety grounds. Based in part on the results of these studies, the satraplatin dosage regimen used in the Phase 3 clinical efficacy study supporting the proposed indication of treatment of hormone refractory prostate cancer was set at 80 mg/m^2 daily for 5 days, repeated every 3 to 5 weeks (see *section III.2.1. Dose response study(ies)*).

Since irreversibly bound drug is not available to distribute to the site(s) of action, efficacy and safety is expectedly related to the concentration of free platinum (i.e., platinum in PUF) instead of total platinum in plasma. No consistent dose-response relationship for myelosuppression could be determined among the clinical studies. In one study, there was a relationship between PUF platinum AUC and reduction in platelet count after a single dose, or between reduction in leukocytes and neutrophils with PUF platinum AUC after 5 days of oral dosing of satraplatin. However, in other studies, no relationship could be ascertained between PUF platinum exposure and myelosuppression after either 5 or 14 days of oral dosing of satraplatin.

Based on theoretic considerations, since platinum-containing species produced by metabolism of satraplatin are believed to be eliminated primarily through the kidney, clearance of these metabolites may be decreased by co-administration of potentially nephrotoxic compounds. This possible interaction is sufficiently worded in section 4.5 of the SPC.

The effect of genetic differences in PD response was not discussed by the APPLICANT. Still, for oxaliplatin , recently a common SNP found for glutathione S-transferase P1 or xeroderma pigmentosum group D enzyme has been suggested to be determinant for the activity of oxaliplatin as well as polymorphisms in the XRCC1 gene have been suggested to have significant impact on the response to platinum-based chemotherapy.
Although DNA repair genes may be expected to affect tumour aggressiveness and/or the outcome of platinum based therapies, sufficient evidence for direct effects of polymorphisms in this repair machinery enzymes, and the subsequent effect on efficacy, is currently lacking. Therefore, it appears premature to include detailed information on this matter in the SPC.

Conclusion:
A major obstacle for sufficiently answering to the concerns raised was the fact that the applicant has not succeeded in the full characterisation of the satraplatin metabolites. In the absence of such metabolism data, questions with regard to involvement of metabolising enzymes and possible polymorphic enzymes, as well as the inhibition potential of satraplatin metabolites, could not be answered. Further characterisation is not to be expected within a reasonable timeframe, and at this stage it is considered not to be a major issue.

Still, a number of issues are considered unresolved, i.e., with respect to the possible inhibition of CYP3A4 in the gut, possible inhibition of CYP450 oxidoreductase and the effect on satraplatin metabolism, and the dose advice for renally impaired patients.

Clinical efficacy

The clinical development program of satraplatin in HRPC consists of five clinical studies, including three Phase III and two Phase II studies. Studies CA142-026, CA142-025, and CA142-029 were terminated early by the original sponsor (BMS) for portfolio management reasons. The Pivotal SPARC study was conducted by GPC Biotech.

Table 1 Clinical development program of satraplatin in HRPC

				Number of patients			
Study	**Phase**	**Line-therapy**	**Dosages**	**Satraplatin**	**Control**	**Total**	**State**
GPC SAT3-03-01 (SPARC)	III	2nd	80 mg/m^2/d x 5d q35d	629	313	942	Completed
CA142-026	II	2nd	80 mg/m^2/d x 5d q 35d	10	0	10	Prematurely terminated
CA142-025 (EORTC 30972)	III	1st	100 mg/m^2/d x5d q 35d	27	23	50	Prematurely terminated
CA142-029	III	1st	100 mg/m^2/d x5d q 35d	7	7	14	Prematurely terminated
CA142-013	II	1st	120 mg/m^2/d x 5d q 21 (28)d	39	0	39	Completed
Total				712	343	1055	

SPARC = Satraplatin and Prednisone against Refractory Cancer; EORTC = European Organisation for Research and Treatment of Cancer

Dose-response studies

No formal dose-response studies of single-agent satraplatin or satraplatin combined with prednisone have been performed in patients with HRPC. The proposed satraplatin oral dose of 80 mg/m^2/day x 5 days every 35 days was selected on the basis of phase I dose-finding trials conducted in patients with various non-hematologic malignancies (but no patients with HPRC were enrolled) (study CA142-002; CA142-012; CA142-003/009) and on the basis of previous studies (study CA142-013; CA142-025; CA142-026; CA142-029) conducted in HPRC and amended for drug toxicity.

The dosing regimen proposed in SPARC study was below the MTD (identified as 140 mg/m^2 in Europe (study 142-002), 100-120 mg/m^2 in the USA (study CA142-003/009) and 120 mg/m^2 in Japan (CA142-012), after 5 consecutive days of oral daily dose, with DLTs of myelosuppression and diarrhea) and was expected to lead to fewer dose reductions and cycles with delay due to drug toxicity than reported in previous studies in HRPC conducted with higher doses (study CA142-013 and CA142-025).

However, only limited experience with satraplatin as 2nd line chemotherapy in patients with HRPC is available: it consists of the Canadian study (CA142-026) that was prematurely stopped by the original sponsor after enrolment of 10 patients. The study specified a starting dose of 100 mg/m^2/day x 5 days every 28 days, but the protocol was amended to a dose of 80 mg/m^2/day every 35 days because 2 of the first 4 patients experienced febrile neutropenia and severe thrombocytopenia.

In conclusion, satraplatin dose justification is based on very limited data. At best tolerance of Satraplatin is not considered as enough to justify the proposed regimen since, although the SPARC study protocol allowed dose escalation after two cycles of therapy, only 10% of the patients received 100 mg after 2 cycles. Therefore, we still do not know if all the patients who could receive a 100 mg dose did received it and what would have been their tolerance profile.

Main clinical studies

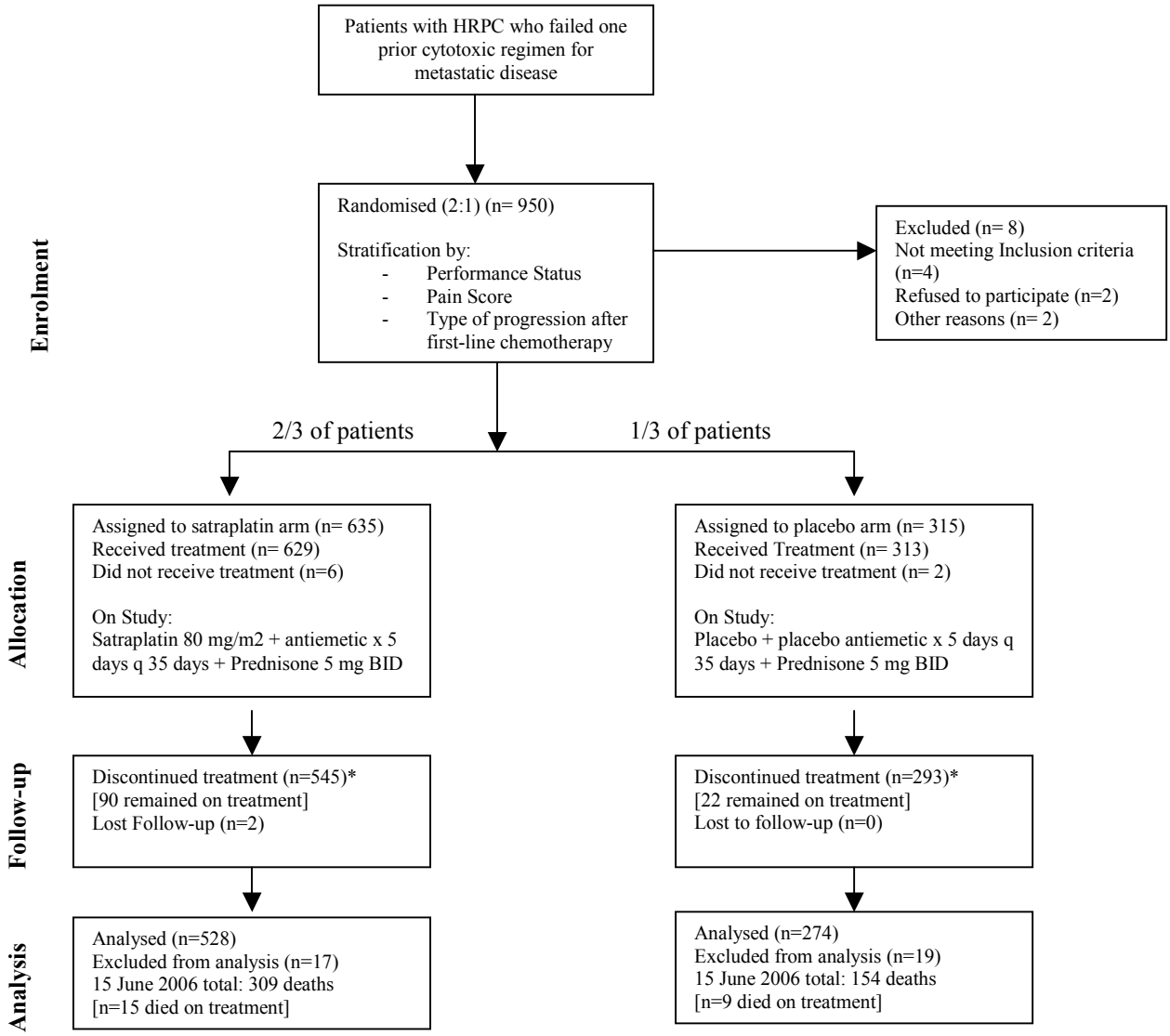
The satraplatin development program in HRPC includes, along with the pivotal SPARC study, two phase II (CA142-013, CA142-026) and two phase III (CA142-025, CA142-029) clinical studies. However, with the exception of study CA142-013, all the other trials have been prematurely terminated by the original sponsor for a business decision. Overall, a total of 113 patients have been treated in these trials (83 with satraplatin and 30 with placebo and/or prednisone), mostly in 1st line chemotherapy. In only 10 patients with HRPC (study CA 142-026) satraplatin was evaluated as 2nd line chemotherapy. Therefore, due to the small simple size and the incomplete data available, no clear indications of satraplatin antitumor activity and safety in the target population can be made from most of these studies. However, in study CA142-025, a significant prolongation in median PFS (5.2 vs. 2.5 months, p=0.023), and a significant increase in PSA response (33% vs. 9%) was reported in a small population of 27 patients treated with satraplatin + prednisone compared with 23 patients receiving prednisone alone, but survival was not significantly improved (14.9 vs. 11.9 months). In study CA142-013, conducted in 39 HRPC patients in 1st line therapy, an overall PSA response rate of 26% (5% RC, 21% PR) was observed; moreover, 1 patient reported partial tumor response and 6 patients stable disease. The number of patients and the data available from the other two studies performed in HRPC (study CA142-026 and study CA142-029) are too limited to allow any meaningful evaluation of the clinical efficacy and safety of satraplatin in the patients treated.

Based on these findings, the Applicant states that, despite the small sample size due to the premature termination of the studies, results suggest a potential activity of satraplatin in HRPC with a manageable toxicity profile. However, truncated studies make any conclusion on efficacy and safety and any interpretation of the clinical benefit hazardous.

GPC SAT3-03-01 (SPARC) Pivotal Study

GPC SAT3-03-01 (SPARC) study is the pivotal randomised, double-blind, placebo-controlled, phase III trial comparing satraplatin plus prednisone versus placebo plus prednisone in 2nd line chemotherapy of advanced HRPC. A total of 950 patients were randomized (2:1) to receive active or placebo oral satraplatin 80 mg/m^2/day for 5 days every 35 days, plus prednisone 5 mg twice daily for 35 days. The SPARC protocol allowed for up to 2 satraplatin dose reductions (from 80 to 60 to 40 mg/m^2/day) for toxicity and delayed recovery due to late hematologic nadirs, and one satraplatin dose escalation from (80 to 100 mg/m^2/day).

As there is currently no approved second line treatment for patients with HRPC who failed taxane-based regimens, the placebo-controlled design of SPARC study is justified and appropriate. The inclusion of relatively low doses of prednisone is acceptable too, because corticosteroids are generally used in palliative setting and have been used in other recent randomized placebo-controlled phase III trials.



*Status as of 15 June 2006

Baseline characteristics (pivotal SPARC study)

A total of 950 patients were randomized into the study, 635 in the satraplatin group and 315 in the placebo group. Patients were stratified based on 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 (PSA progression versus tumor progression on prior cytotoxic therapy). No stratification by participant centre neither by geographical area as well as by type of prior treatment (in particular docetaxel use) or duration of prior progression has been done.

The study population was similar to the general patient population with advanced HRPC in several aspects. The population included symptomatic and asymptomatic patients and the median age was 70 years (range, 42-95 yr). The majority of patients were Caucasian (88.5%) and most commonly presented with advanced disease at initial diagnosis (≥ Jewett stage D2 or Gleason Scores ≥ 5). However, only 36% had substantial pain (PPI 2-5) and around 90% had good ECOG performance status (≤ 1). Moreover, as SPARC study started before the approval of docetaxel in 1st line therapy of HRPC, only 51.4 % of patients enrolled were pre-treated with docetaxel. Considering that currently docetaxel is the standard 1st line therapy in HRPC, this implies that only around one-half of the population studied fulfilled the pre-requisite for the claimed indication.

Moreover, around 10% of patients received only one line of hormonal therapy before entry in SPARC study. In addition, for around 6% of patients treated in SPARC study it is not clear if they met the criteria of HRPC definition, since no concomitant LHRH agonist use was reported in the CRF of these patients. However, they represented a relatively small percentage of the total patient population and that they were balanced between study groups.

In general, there were no obvious imbalances between the satraplatin and the placebo arms in any of demographic and baseline characteristic evaluated, in particular no significant difference were found in terms of age, distribution of poor prognostic factors (hemoglobin, LDH, alkaline phosphatase, ECOG PS, and creatinine clearance), prior cancer therapy, type of prior chemotherapy, type of disease progression, and time from disease progression to randomization into SPARC study (Table 2). Moreover, there were no obvious imbalances between the satraplatin and placebo arms for concomitant medical conditions and physical findings.

Table 2 Demographic and Baseline characteristics in SPARC study - Prior Treatment for Prostate Cancer: ITT Population

	Number (%) of Patients					
Parameter	Satraplatin (N=635)		Placebo (N=315)		Total (N=950)	
Type of Prior Therapy for Prostate Cancer						
Surgery (excluding biopsy)	365	(57.5)	176	(55.9)	541	(56.9)
Radiotherapy	381	(60.0)	186	(59.0)	567	(59.7)
Hormonal Therapy	624	(98.3)	308	(97.8)	932	(98.1)
Chemotherapy[a]	52	(8.2)	25	(7.9)	77	(8.1)
Immunotherapy	19	(3.0)	7	(2.2)	26	(2.7)
Prednisone	242	(38.1)	115	(36.5)	357	(37.6)
Prior Cytotoxic Regimen	635	(100.0)	315	(100.0)	950	(100.0)
Prior Cytotoxic Therapy[b]						
Docetaxel	327	(51.5)	160	(50.8)	487	(51.3)
Estramustine	265	(41.7)	137	(43.5)	402	(42.3)
Mitoxantrone	128	(20.2)	64	(20.3)	192	(20.2)
Paclitaxel	17	(2.7)	9	(2.9)	26	(2.7)
Duration of Prior Cytotoxic Therapy						
N	635		315		950	
Median	20.6 weeks		19.6 weeks		20.4 weeks	
(min, max)	(0.4-381.6)		(3.0-231.7)		(0.4-381.6)	
Time from End of Prior Therapy to Randomization						
N	635		315		950	
Median	10.0 weeks		9.6 weeks		10.0 weeks	
(min, max)	(0.1-291.6)		(0.0-209.9)		(0.0-291.6)	
Time from Prior Disease Progression to Randomization						
N	633		314		947	
Median	4.6 weeks		5.0 weeks		4.9 weeks	
(min, max)	(0.1-134.4)		(0.1-110.6)		(0.1-134.4)	
Type of Prior Progression[c]						
Radiographic	344	(54.2)	178	(56.5)	522	(54.9)
Radiographic (Confirmed)	308	(48.5)	157	(49.8)	465	(48.9)
PSA Rise	595	(93.7)	297	(94.3)	892	(93.9)
PSA Rise (Confirmed)	466	(73.4)	243	(77.1)	709	(74.6)
PSA Rise Only	290	(45.7)	136	(43.2)	426	(44.8)
Missing	1	(0.2)	1	(0.3)	2	(0.2)

[a] Excluding prior cytotoxic chemotherapy regimen.

[b] Due to use of combination regimens, there can be overlap between the categories for prior cytotoxic treatments.

[c] Prior progression data based on data collected in the CRF, not data collected at randomization through IVRS.

KEY: ITT=intent-to-treat, max=maximum, min=minimum, N=number of patients evaluated, PSA=prostate specific antigen

Table 3 Demographic and Baseline Characteristics: ITT Population

Demographic Characteristic	Number (%) of Patients					
	Satraplatin (N=635)		Placebo (N=315)		Total (N=950)	
Age						
N	635		315		950	
<65 years	180	(28.3)	93	(29.5)	273	(28.7)
≥65 years	455	(71.7)	222	(70.5)	677	(71.3)
≥75 years	167	(26.3)	85	(27.0)	252	(26.5)
Median (min, max)	70	(42-88) yr	68	(45-95) yr	70	(42-95) yr
Race						
Caucasian	559	(88.0)	282	(89.5)	841	(88.5)
Black	26	(4.1)	17	(5.4)	43	(4.5)
Latin American	43	(6.8)	13	(4.1)	56	(5.9)
Other[a]	7	(1.1)	3	(1.0)	10	(1.1)
Geographic Region						
North America[b]	180	(28.3)	81	(25.7)	261	(27.5)
Europe & Israel[c]	372	(58.6)	196	(62.2)	568	(59.8)
South America[d]	83	(13.1)	38	(12.1)	121	(12.7)
ECOG PS[e]						
ECOG 0-1	563	(88.6)	285	(90.5)	848	(89.3)
ECOG ≥2	72	(11.3)	30	(9.5)	102	(10.7)
Hemoglobin						
≥11.0 g/dL	491	(77.3)	253	(80.3)	744	(78.3)
<11.0 g/dL	142	(22.4)	62	(19.7)	204	(21.5)
Missing	2	(0.3)	0	(0.0)	2	(0.2)
LDH						
<2 × ULN	516	(81.3)	260	(82.5)	776	(81.7)
≥2 × ULN	58	(9.1)	31	(9.8)	89	(9.4)
Missing	61	(9.6)	24	(7.6)	85	(8.9)
Alkaline Phosphatase						
<1.5 × ULN	374	(58.9)	188	(59.7)	562	(59.2)
≥1.5 × ULN	250	(39.4)	124	(39.4)	374	(39.4)
Missing	11	(1.7)	3	(1.0)	14	(1.5)
Calculated Creatinine Clearance						
>50 mL/min	584	(92.0)	290	(92.1)	874	(92.0)
≤50 mL/min	50	(7.9)	24	(7.6)	74	(7.8)
Missing	1	(0.2)	1	(0.3)	2	(0.2)
Malignant Lesion Type (Investigator Assessment)						
At Least One Target Lesion[a]	320	(50.4)	169	(53.7)	489	(51.5)
Non-Target Lesions[b] Only	310	(48.8)	144	(45.7)	454	(47.8)
Missing	5	(0.8)	2	(0.6)	7	(0.7)
Calculated PPI Score[c]						
N	613		298		911	
PPI 0	226	(36.9)	101	(33.9)	327	(35.9)
PPI 1	161	(26.3)	97	(32.6)	258	(28.3)
PPI 2-5	226	(36.9)	100	(33.6)	326	(35.8)
Calculated Analgesic Score						
N	617		299		916	
Median	0.0		0.0		0.0	
Range (min, max)	(0.0-215)		(0.0-136)		(0.0-215)	
Prostate Specific Antigen (ng/mL)						
N	630		313		943	
Median	140		134		138	
Range (min, max)	(0.1-6084)		(0.1-7059)		(0.1-7059)	
Ongoing Bisphosphonate Therapy						
N	635		315		950	
Yes	440	(69.3)	229	(72.7)	669	(70.4)
No	195	(30.7)	86	(27.3)	281	(29.6)

a Includes Asian and other ethnicities.
b Includes US (258 patients accrued) and Canada (3).
c Includes Belgium (46 patients accrued), Croatia (24), France (141), Germany (61), Hungary (22), Israel (14), Italy (23), The Netherlands (11), Poland (71), Russia (28), Spain (42), and UK (85).
d Includes Argentina (98 patients accrued) and Peru (23).
e ECOG performance status is based on data collected in the CRF rather than data collected at screening through IVRS.
KEY: CRF=case report form, ECOG=Eastern Cooperative Oncology Group, ITT=intent-to-treat, IVRS=interactive voice response system, LDH=lactate dehydrogenase, max=maximum, min=minimum, PS=performance status, ULN=upper limit of normal.

Most importantly, according with the data provided in the Applicant's response to the CHMP day 120 List of Questions, 15.6% (148/950) of patients enrolled in SPARC study presented major protocol violation. This is considered not negligible, especially when considering the item "inclusion/exclusion criteria not met" (35.8% of excluded patients [53/148] overall, and 39.2% [40/102] in the Satraplatin group).

Major Protocol Violations: Patients Excluded From the Per-Protocol Population (SPARC study)

Violation	Number (%) of Excluded Patients		
	Satraplatin (N=102)	Placebo (N=46)	Total (N=148)
Inclusion/exclusion criteria not met	40 (39.2)	13 (28.3)	53 (35.8)
Initial procedure prior to signed informed consent	9 (8.8)	9 (19.6)	18 (12.2)
No scans/x-rays within 28 days of study therapy	11 (10.8)	6 (13.0)	17 (11.5)
Pain unstable at baseline	9 (8.8)	7 (15.2)	16 (10.8)
2 prior chemotherapy regimens	7 (6.9)	2 (4.3)	9 (6.1)
Other malignancy	7 (6.9)	1 (2.2)	8 (5.4)
Undocumented castration	3 (2.9)	4 (8.7)	7 (4.7)
Delayed cycle	7 (6.9)	0 (0.0)	7 (4.7)
Prior radiopharmaceuticals	2 (2.0)	1 (2.2)	3 (2.0)
Serum creatinine level >1.2 x ULN	2 (2.0)	1 (2.2)	3 (2.0)
Undocumented D2 tumor	2 (2.0)	1 (2.2)	3 (2.0)
Bisphosphonate started at randomization	1 (1.0)	1 (2.2)	2 (1.4)
No creatinine within 21 days of study therapy	1 (1.0)	0 (0.0)	1 (0.7)
No hematology within 21 days of study therapy	1 (1.0)	0 (0.0)	1 (0.7)

Note: Patient counts within categories of violations represent the primary reason for exclusion from the per-protocol population. Data in table based on cut-off date of 21-Sep-2007.
KEY: ULN=upper limit of normal

Methodology (pivotal SPARC study)

The statistical hypothesis provided for superiority of the primary objectives in treatment arm compared with control arm. Co-primary objectives were Progression Free Survival (PFS) and Overall Survival (OS). Secondary endpoint was time-to-pain progression (TPP). Other exploratory endpoints were pain response and PSA response as well as the assessment of satraplatin's safety in this setting.

However, the definition of PFS as adopted in SPARC study needs further considerations. PFS was measured from the date of randomisation to the date of disease progression or death, censored at the last tumor evaluation date. Disease progression was defined as a composite endpoint based on the first occurrence of the following:

- tumor radiographic progression (based on RECIST criteria for soft tissues and bone scans for bone lesions);
- progression related to skeletal events;
- symptomatic progression (increase in pain, increase in ECOG performance status, decrease in weight, or other clinical events – such as bladder outlet or ureteral obstruction or symptomatic spinal cord compression - attributable to prostate cancer in the investigator's opinion);
- death.

An increase in PSA was not part of this progression endpoint. The decision not to include PSA in the definition of PFS as doubtful due to the fact that PSA was assessed prior to each cycle allowing therefore potential bias.

Of note, new lesions on bone scan in the presence of improvement of PSA and/or symptoms were not considered progressive disease.

The composite definition of PFS (and in particular of disease progression) as intended in the SPARC trial has not been used previously in a registration study. Moreover this definition of PFS can potentially be subject to investigator bias, also considering that the adverse events expected with satraplatin may have compromised the double-blind nature of the study. Finally, for calculation of the analgesic score and subsequent symptomatic progression (as part of composite PFS) only narcotic analgesics were counted, whereas it is recognized that the use of narcotic analgesics varies widely between different countries. In addition, no plan for pain management was provided by the SPARC study protocol.

The Applicant justifies the composite PFS employed in SPARC study saying that it was designed to incorporate a wide spectrum of disease characteristics in order to be able to demonstrate clinically relevant benefit in the target population. Moreover, the Applicant states that each of the components of the endpoint can be considered validated in its own right and each has been used in previous registrational studies. However, the fact that each of the components of the composite PFS endpoint has been used in previous registrational studies in other indications does not necessary make the composite PFS as defined in SPARC a parameter able to prove clinical benefit for the HRPC population. Finally, the guidelines from the Prostate Cancer Clinical Trials Working Group (PCWG) mentioned by the Applicant to further support the validity of the composite PFS are aimed to maximize the ability of phase II trials to screen or select promising therapies, and they only recommend "increasing emphasis on time-to-event end points as decision aids in proceeding from phase II to phase III trials". Indeed, the guidelines introduce the concept of PFS as composite endpoint, and they encourage "the incorporation of similar parameters into phase III

trials assessing overall survival in order to generate the databases that will allow validation or refinement of the intermediate endpoints".

The original submission for MAA (Marketing Authorization Application) was based upon final analysis of PFS data (802 events) and interim results on OS (cut-off date: 15 June 2006). In the Applicant's response to the CHMP day 120 List of Questions final results on OS of SPARC study were provided (cut-off date: 21 September 2007).

Efficacy (pivotal SPARC study)

Co-Primary Objective: Progression Free Survival (PFS) (pivotal SPARC study)

The analysis is based 802 observed events, 528 patients (83.1%) in satraplatin group and 274 patients (87%) in placebo group. According to the Statistical Analysis Plan only 694 PFS were required. Progression was determined by investigators and by an independent committee of experts in a blinded fashion (IRC). Overall, 81% of the PFS events (649/802) consisted of radiographic progression (290/802 patients, 36.2%), pain progression (298/802 patients, 37.2%) or death (61/802 patients, 7.6%) (Table 4). Comparable proportions of patients had radiographic progression in both arms (35.8% *vs.* 36.9%), but there were relatively less pain progressions in the satraplatin arm than in the placebo arm (34.3% *vs.* 42.7%). Of note, progression due to skeletal-related events was significantly higher in satraplatin (22/528 patients, 4.2%) compared with placebo group (5/274 patients,1.8%).

Table 4 PFS Events (IRC Defined): ITT Population (SPARC study)

	Number (%) of Patients					
	Satraplatin		Placebo		Total	
Parameters	(N=635)		(N=315)		(N=950)	
PFS Events, n/N (%)	528/635	(83.1)	274/315	(87.0)	802/950	(84.4)
Tumor Progression	211/528	(40.0)	110/274	(40.1)	321/802	(40.0)
Radiology	189/528	(35.8)	101/274	(36.9)	290/802	(36.2)
Clinical	22/528	(4.2)	9/274	(3.3)	31/802	(3.9)
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)
PS	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*	36/528	(6.8)	14/274	(5.1)	50/802	(6.2)
Death without any prior progression events	48/528	(9.1)	13/274	(4.7)	61/802	(7.6)

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

NOTE: Data in table based on cut-off date of 21-Sep-2007.

KEY: IRC=independent review committee, ITT=intent-to-treat, PFS=progression-free survival. PS=performance status

The comparison between investigator and IRC assessments of progression showed overall concordance on 83.8% of progression events in the satraplatin group and 91.4% in the placebo group. However, the concordance level for the assessment of radiographic progression was significantly lower (69.8% in the satraplatin and 70.8 % in the placebo group).

The analysis on PFS for the ITT population (as adjudicated by the IRC), showed a statistically significant difference between the progression free survival curves ($p<0.001$ at log-rank test) and the mean PFS was 24.9 weeks in the satraplatin arm vs. 16.2 weeks in the placebo arm. A significant 33% reduction in risk of progression for satraplatin compared with placebo was found (HR=0.67, 95% CI: 0.57, 0.77, $p<0.001$). However, the difference in median PFS between the two arms was only 9.8 days, which is clearly not statistically significant and not clinically relevant (median PFS satraplatin: 11.1 weeks, placebo: 9.7 weeks). Looking at the Kaplan Meier curves, the difference between satraplatin and placebo curves becomes mostly apparent after two courses (~ 10 weeks) of therapy: that time corresponds to the official first re-evaluation by imaging after randomization and, of note, at that time around one-half of the patients already had progression (Table 5).

Table 5 Progression-Free Survival Analysis for the Intent-to-Treat Population

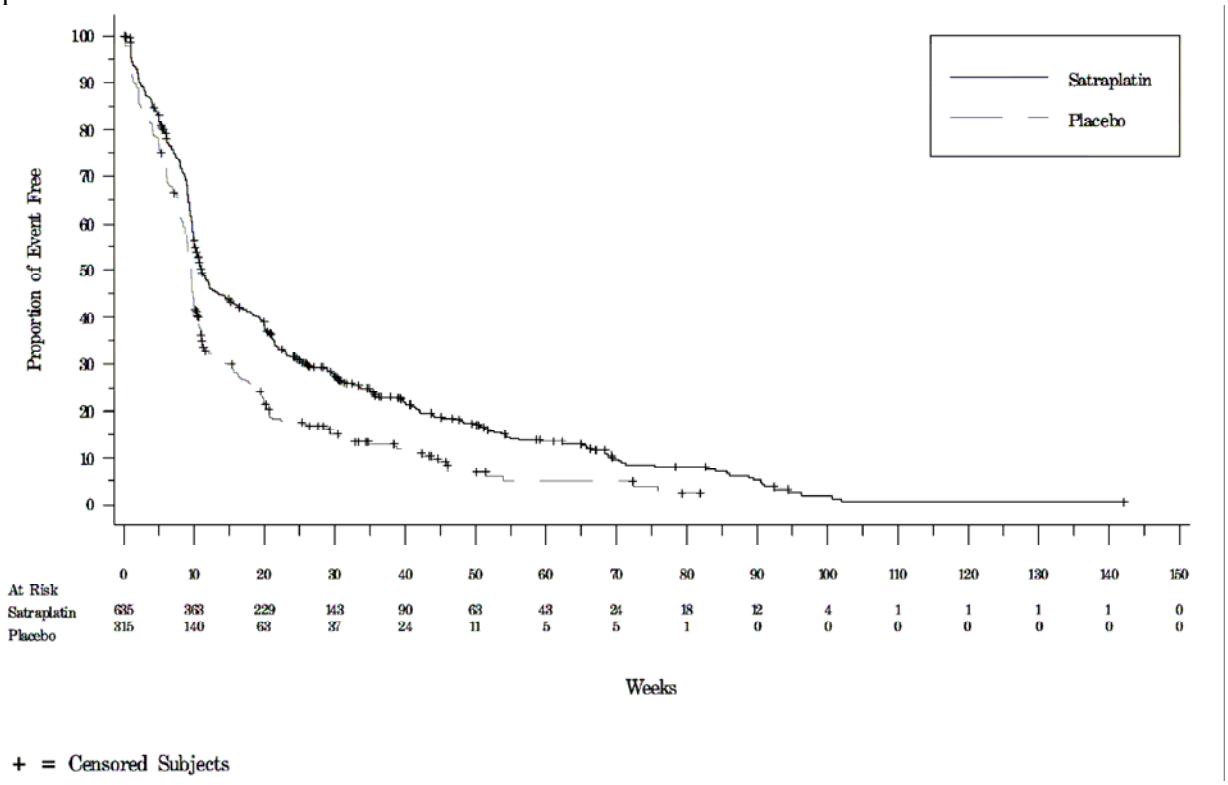
Analysis	Satraplatin (N=635)	Placebo (N=315)
PFS by IRC – ITT Population		
PFS Events, n (%)	528 (83.1)	274 (87.0)
25th Percentile	7.3 weeks	5.4 weeks
Median	11.1 weeks	9.7 weeks
75th Percentile	34.6 weeks	19.1 weeks
PFS Probability		
Month 6	0.30 (0.019)	0.17 (0.022)
Month 12	0.16 (0.017)	0.07 (0.018)
Log Rank p-value[a]	<0.001	
HR (95% CI)[b]	0.67 (0.57, 0.77)	
Mean (SE) weeks	**24.9 (1.2) weeks**	**16.2 (1.2)**

[a] Stratified log-rank test.

[b] Cox proportional hazards model with covariates for PS, PPI, and type of prior progression.

KEY: CI=confidence interval, HR=hazard ratio, IRC=independent review committee, ITT=intent-to-treat, PFS=progression-free survival, PPI=present pain intensity, PS=performance status

Figure 1 Kaplan Meier plot of Progression-Free Survival (as adjudicated by the IRC) for the ITT Population



According to the Applicant, when PFS was analyzed by the individual components treatment benefits were observed in the subset of patients with radiographic progression or death (HR=0.64; 95% CI: 0.51, 0.81) and the subset of patients with pain progression or death (HR=0.64; 95% CI: 0.51, 0.79). Radiographic progression and pain progression together account for 73.4% of PFS events (70.1% satraplatin and 79.6% in the placebo arm).

In the Applicant's response to the CHMP day 120 List of Questions, in the justification over the clinical relevance of the PFS results, the Applicant argued that the best method for presenting the treatment benefit for satraplatin over placebo is the Kaplan-Meier curves and that the hazard ratio is the most appropriate

summary statistic to present treatment benefit, since it represents an average over the entire PFS distribution. However, it should be noted that, from a statistical point of view, as a consequence of the fact that at the time of first re-evaluation of the patients by imaging after randomization (10 weeks) around one-half of the patients already had progression, single summary statistics describing an "overall treatment benefit" such as the hazard ratio and the mean, as well as log-rank test cannot lead to a reliable clinical interpretation, because their magnitude is mainly driven by the difference in PFS distributions after 10 weeks. Indeed, the hazard ratio of 0.67 (95% CI: 0.57, 0.77) does not automatically translate into a clinical benefit for all the population, since the magnitude of progression risk reduction is mainly determined by the difference in PFS curves observed after 10 weeks.

Co-Primary Objective: Overall Survival (OS) (SPARC study)

In the Applicant's response to the CHMP day 120 List of Questions final results on overall survival (OS) based on the 713 deaths present in the database as of the cut-off date of 21 September 2007 were provided. The final analysis of OS showed no difference between the survival curves for satraplatin compared to placebo (HR=0.97; 95% CI: 0.83, 1.13). The median survival in both treatment groups was 61 weeks (approximately 15 months).

Figure 2 Final Overall Survival Analysis for the ITT population in SPARC study

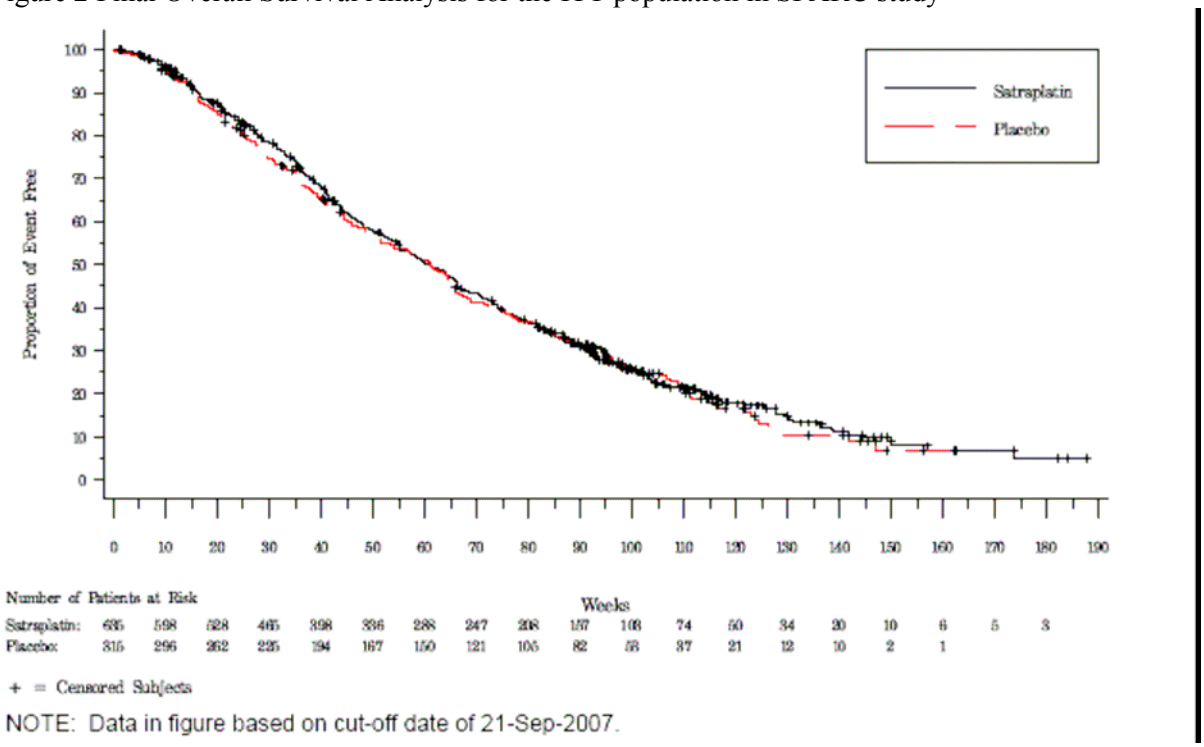


Table 6. Final Overall Survival Analysis for the ITT population in SPARC study

Analysis	Satraplatin (N=635)	Placebo (N=315)
OS – ITT Population		
Death Events, n (%)	474 (74.6)	239 (75.9)
Median, weeks	61.3	61.4
Log-rank p-value [a]	0.799	
HR (95% CI) [b]	0.97 (0.83, 1.13)	

[a] Log-rank test with IVRS stratification: IVRS Performance status, IVRS pain, and IVRS progression type

[b] Cox proportional hazards model with covariates for baseline PS, baseline PPI, and type of prior progression.

NOTE: Data in table based on cut-off date of 21-Sep-2007.

KEY: CI=confidence interval, HR=hazard ratio, ITT=intent-to-treat, IVRS=interactive voice response system, OS=overall survival, PPI=present pain intensity, PS=performance status

Secondary and Exploratory Objectives

In the evaluation of secondary and other endpoints it is important to note that they are considered exploratory and not supportive for a marketing claim because in the final analysis plan (version 2 dated March 2006) only a hierarchical testing procedure for OS and PFS was provided. No further plans to adjust for multiplicity or ordering of other endpoints was mentioned. Moreover, only a portion of patients enrolled were eligible for evaluation for any one of these secondary endpoints. Finally, the results of endpoints related to pain response and time to pain progression are basically biased by the lack of evaluation of the use of non-narcotic analgesics by the patients.

Secondary objective: Time-to-pain progression (TPP)

Time-to-pain progression was defined as the time from randomization to the first observed pain related progression that had been confirmed, as adjudicated by the IRC. PPI in the ITT population was significantly longer in satraplatin arm compared with the placebo arm, with means of 53.0 weeks *vs.* 36.6 weeks, respectively. A 36% reduction in the risk of pain progression associated with satraplatin therapy was reported (HR=0.64; 95% CI: 0.51, 0.79; p<0.001).

Exploratory end-points:

Pain Response and Response Duration

Data were updated since the initial MAA, using a data cut-off date of 21 September 2007. Of note, only 354 patients in satraplatin and 185 patients in placebo arm had pain at baseline, and analgesic use determined and at least 4 consecutive weekly assessments of PPI and analgesic score from the period after initiation. Of them, a higher percentage of patients receiving satraplatin compared to those receiving placebo achieved a pain response (25.1% [89/354] vs. 14.1% [26/185], p=0.0028). A trend versus longer response duration in patients receiving satraplatin (median 42 weeks) versus patients receiving placebo (median 26.1 weeks) was also reported by the Applicant, but the difference was not statistically significant (p=0.0883, HR 0.55, 95% CI: 0.30, 1.04).

Tumor Response and Tumor Response duration

Tumor response was assessed according to RECIST criteria. Among patients with an IRC defined soft tissue lesion (352 in the satraplatin and 177 in the placebo group), objective tumor responses, defined as complete (CR) and partial responses (PR), were significantly higher in patients treated with satraplatin compared to placebo (6.5% [0 CR + 23 PR] in satraplatin *vs*. 0.6% [1 CR + 0 PR] in placebo group, p=0.001). However, no complete response was observed in satraplatin arm. The mean (± SE) duration of tumor response in the satraplatin group was 58.7 (± 5.8) weeks; the median was 63.3 weeks.

PSA response
PSA response rate was significantly higher in satraplatin compared with placebo group (25.4% [121/476 pz] *vs.* 12.4% [28/225 pz], respectively, p<0.001 by Fisher's exact test). Data are lacking on the number of patients with complete or partial PSA response in the two arms of the study. Moreover, duration of PSA response was not significantly different between the two arms of the study (41 vs. 40.6 weeks). However, according to the Applicant, the difference between the two groups in median time-to-PSA progression was significant (satraplatin: 35.6 weeks; placebo: 25.1 weeks, log rank p-value=0.006). There was also a 33% reduction in the risk of PSA progression associated with satraplatin therapy (HR=0.67; 95% CI: 0.51, 0.87). However, the percentage of patients with PSA progression was higher in the satraplatin (37%) than in the placebo group (30%).

Table 7. Results of Secondary and Exploratory Endpoints in SPARC study

	Satraplatin	Placebo	p- value	HR (95% CI)
Mean TPP (±SE) (weeks)	53.0 (2.3)	36.6 (2.7)	< 0.001	0.64 (0.51, 0.79)
Pain Response	25.1% (89/354)	14.1% (26/185)	0.0028	-
Tumor Response (CR+PR)	6.5% (23/352)	0.6% (1/171)	0.001	-
PSA Response	25.4% (121/476)	12.4% (28/225)	0.001	-

TPP: Time-to-Pain Progression; SE: Standard Error; HR: Hazard Ratio.

Ancillary analyses

- Sensitivity analyses
A series of sensitivity analyses were performed by the Applicant to explore the potential effects of assessment bias and potential differences between investigator and IRC judgments in the evaluation of PFS, according also with the EMEA draft guidance "Methodological Considerations for Using Progression-free Survival (PFS) as Primary Endpoint in Confirmatory Trials for Registration" and other regulatory guidance documents on clinical trial conduct for oncology agents. Sensitivity analyses have been performed addressing 4 points: Cycle lengths for the satraplatin and placebo groups; Individual components within the Composite Endpoint; Association between the investigator and IRC determined events of disease progression; Follow-up for censoring. The Applicant states that the results of these analyses are consistent with the treatment effect observed in the primary analysis of PFS. However, they did not resolve major concerns about the claimed clinical relevance of the difference between the treatment arms and the validity of the composite PFS.

- Post-hoc analyses
The Applicant states that post-hoc sensitivity analyses were designed as "worst case" scenarios with a bias against the satraplatin group in order to further demonstrate the robustness of the PFS results. Several post-hoc analyses were performed to:

- compare the effects of treatment between the ITT population and the subset without or with (51.4% of ITT) prior exposure to docetaxel;
- compare the effects of treatment among the ITT population subset symptomatic and asymptomatic, as defined by baseline average PPI score = 1-5 and 0, respectively;
- confirm that results obtained from the North American subset (27% of the total study population) were representative of those for the ITT population;
- compare results between the ITT and the Per-Protocol populations.

The Applicant states that the results of efficacy analyses for all the subsets analyzed were similar to those observed for the ITT population in terms of PFS, OS, TPP.

- Subgroup analyses: OS and PFS by pre- or post- SPARC chemotherapy

In the response to the CHMP day 120 List of Questions the Applicant provided the results of subgroup analyses over Overall Survival by pre- or post- SPARC chemotherapy and PFS by prior or no prior use of docetaxel[A2]..Of note, although prior docetaxel use was not a stratification factor, the treatment arms were well balanced in this respect (51.5% [327/635] vs. 51.1% [161/315]). However, a higher proportion of patients in the placebo arm received docetaxel after SPARC than in the satraplatin arm (18.6% [118/635] vs. 25.1% [79/315]) (Table 8). Moreover, an imbalance in the proportion of patients who received any post-SPARC chemotherapy, with a higher percentage of placebo patients (55%) than satraplatin patients (45%) receiving 3rd line chemotherapy, was observed.

Table 8 Overall Summary of Docetaxel Use (SPARC study)

Number (%) of Patients					
Satraplatin (N=635)			Placebo (N=315)		
Prior Docetaxel Only	Post-SPARC Docetaxel Only	Prior and Post-SPARC Docetaxel[a]	Prior Docetaxel Only	Post-SPARC Docetaxel Only	Prior and Post-SPARC Docetaxel[a]
288 (45.4%)	80 (12.6%)	39 (6.1%)	134 (42.5%)	52 (16.5%)	27 (8.6%)

* Patients who received docetaxel only prior to SPARC or only post-SPARC are not included in this column.

NOTE: Data in table based on cut-off date of 21-Sep-2007.

Table 9 Overall Survival by pre- or post- SPARC chemotherapy and PFS by prior or no prior use of docetaxel

	Median Overall Survival (weeks)		Log-rank p-value	HR (95% CI)
	Satraplatin	Placebo		
ITT Population	61.3	61.4	0.799	0.97 (0.83, 1.13)
Prior-docetaxel	66.1	62.9	0.399	0.91 (0.73, 1.14)
No Prior-docetaxel	58.0	58.6	0.784	1.03 (0.82, 1.28)
Post SPARC docetaxel	90.4	92	0.602	0.91 (0.65, 1.27)
Any Post SPARC chemotherapy	77.3	77.0	0.903	0.96 (0.77, 1.19)
No Post SPARC chemotherapy	41.9	35.7	0.206	0.84 (0.67, 1.06)
No or other than docetaxel Post SPARC chemotherapy	53.6	51.3	0.420	0.91 (0.77, 1.09)
	Median PFS (weeks)			
ITT Population	11.1	9.7	< 0.001	0.67 (0.57, 0.77)
Prior docetaxel	10.1	9.1	< 0.001	0.67 (0.54, 0.82)
No Prior docetaxel	12.3	10.1	< 0.001	0.67 (0.54, 0.83)

The results of the analyses (Table 9) showed neither a statistically significant nor a clinically relevant difference in Overall Survival between satraplatin and placebo arms in all the subgroups of the population analyzed. Although a trend towards a benefit for satraplatin in patients who didn't receive an effective post-study treatment has been claimed by the Applicant, the results presented in Table 9, the imbalance observed between the two study arms regarding the percentage of patients who received post study chemotherapy and the fact that the subgroup analyses performed were not planned make any conclusion over a survival benefit of satraplatin in this subgroup of the population not acceptable.

Regarding PFS results, the results of subgroup analyses by previous treatment with docetaxel were similar to the overall population: although a statistically significant reduction in the risk of disease progression associated with satraplatin treatment was observed, the difference between the two study groups in median PFS was not statistically significant and not clinically relevant.

Clinical studies in special populations

In the response to the CHMP day 120 List of Questions the Applicant provided the final results of two phase I studies (**SAT1-04-04** and **SAT1-04-03**) conducted in patients with non-hematological malignancies and evaluating the effect of various degrees of hepatic and renal impairment, respectively, on satraplatin pharmacokinetics, disposition and safety. A total of 32 patients divided in 4 cohorts (each containing 8 patients) defined by level of hepatic or renal impairment, respectively, were treated with satraplatin. In study SAT1-04-04, 9 patients (9/27, 33.3%) reported stable disease and 9 patients (9/27, 33.3%) reported progressive disease (PD). In study SAT1-04-03, 1 patient (1/24, 4.2%) reported partial response, 5 patients (5/24, 20.8%) reported stable disease, and 10 patients (10/24, 41.7%) reported progressive disease. However, the sample size of each cohort was clearly too little to allow any meaningful evaluation of the efficacy and safety of satraplatin in these special populations. The pharmacokinetic findings and the safety results of both two studies are reported in the pharmacokinetic and safety section, respectively, of the present Overview.

Clinical safety

Patient exposure

As of 15 June 2006, a total of 1260 patients had received satraplatin in 29 clinical studies. This population included 712 patients with HRPC, of whom 629 were treated in the SPARC study, 56 participated in the Prostate Pool studies (consisting of study CA142-013, CA142-026 and CA142-029), and 27 were exposed to satraplatin in the EORTC 30972 study. A total of 317 patients were treated with satraplatin for other (non-HRPC) indications (15 clinical studies), and 231 patients with advanced solid tumors received the drug in 9 pharmacology/pharmacokinetic studies (Table 10). In 2 of these studies (still ongoing), satraplatin was administered to patients with non-hematological malignancies and varying degrees of hepatic (study SAT1-04-04) and renal (study SAT1-04-03) impairment.

In the 29 clinical studies overall, the majority of patients received satraplatin doses between 80 and 120 mg/m^2/day; smaller numbers of patients received doses ranging between 5 and 75 mg/m^2/day or between 124 and 700 mg/m^2/day. The starting dose for all patients in the SPARC study was 80 mg/m^2/day for 5 days per cycle. In SPARC study, patients in the satraplatin group had greater drug exposure than in the placebo group, based on a median of 4 cycles (range: 1-28) compared to 2 cycles (range: 1-16) of treatment, respectively, at median relative dose intensity of 95.6% and 97.8%, respectively, relative to the planned dose. The most common modifications of satraplatin treatment included 1 dose delay ≥7 days (39.4%) and dose reductions (19.7%).

Table 10 Overall Extent of Exposure to Study Drug

		Extent of exposure to study drug			Exposure to satraplatin by dose		
		N. Patients			N. Patients		
Study Type	N. Studies	Dosage(s)	Satraplatin	Control[g]	<80 mg/m^2/day	80 to 120 mg/m^2/day	>120 mg/m^2/day
Clinical Pharmacology/ Pharmacokinetic Studies[a]	9	10 to 700 mg/m^2/day	231	0	74	109	50
HRPC Studies	5	80 to 120 mg/m^2/day	712	343	-	712	-
SPARC[b]	1	80 mg/m2/day	629	313	-	629	-
Prostate Pool[c,f]	3	80 to 120 mg/m^2/day	56	7	-	56	-
EORTC 30972[b]	1	100 mg/m2/day	27	23	-	27	-
Other Clinical Studies[d]	15	5 mg/day to 120 mg/m^2/day	317	49	191[e]	142	18
Total	29		1260	392	265	963	68

[a] Data are based on the intended dose and subsequent dose escalation and reductions, which occurred in one patient each.
[b] In the SPARC and EORTC 30972 studies, the intended doses were 80 mg/m2/day and 100 mg/m2/day, respectively.
[c] Data are based on the maximum dose received during the study.
[d] Data are based on starting doses in the first cycle and subsequent dose reductions/increases.
[e] This includes a total of 55 patients (Studies CA142-031, CA146-013, CA142-016 and CA142-020) whose dose was not based on body surface area, but was ≤ 30 mg/day.
[f] Prostate Pool includes 2nd line HRPC studies CA142-013 (n=39), CA142-026 (n=10), and 1st line HRPC study CA142-029 (n=7).
[g] Control: placebo + prednisone in study CA142-029 and SPARC study; prednisone in EORTC 30972; cisplatin in study CA142-008; cisplatin or carboplatin in study CA142-006.

Adverse events

In SPARC study, most patients (91.4% in the satraplatin group and 81.8% in the placebo group) reported at least one TEAE (Table 11). More patients in the satraplatin group than in the placebo group reported Grade 3 or 4 TEAEs (52.9% vs. 29.7%), treatment emergent serious adverse events (SAEs, 25.8% vs. 16.6%), TEAEs requiring new or prolonged hospitalization (23.8% vs. 15.0%), and TEAEs leading to discontinuation of study drug (13.5% vs. 8.6%). However, both treatment groups had a similar percentage of TEAEs with an outcome of death (3.0% vs. 3.5%).

A higher percentage of patients in the satraplatin group compared to the placebo group had study-drug related AEs—considered by the investigator to be possibly, probably, or definitely related to study drug—of any grade (78.9% vs. 36.7%) or Grade 3 or 4 (34.3% vs. 5.8%). The satraplatin group also had a higher percentage of study-drug related SAEs (8.7% vs. 3.2%).

Consistent with the expected pharmacology of the drug, TEAEs reported in ≥10.0% of patients in the satraplatin group were primarily hematological (thrombocytopenia (32%), neutropenia (28.3%), and anemia (24%)) and gastrointestinal (nausea (28.8%), diarrhea (23.8), constipation (22.7%), and vomiting (16.4%)) adverse events. Fatigue (17.5%), asthenia (14.9%), bone pain (12.6%), anorexia (12.1%), back pain (11.9), and arthralgia (11.6%) were also reported in ≥10.0% of patients in the satraplatin group. Hematological and gastrointestinal events and fatigue were reported at a greater incidence in the satraplatin arm compared with the placebo arm. Of note, drug hypersensitivity was reported in 1.1% (7/629) of patients in the satraplatin group. The incidence of renal failure was limited (1.4% in SPARC study) but serious adverse events and deaths related to renal failure were reported as study-drug related. Neurotoxicity and ototoxicty were rare and of mild or moderate severity.

Table 11 Most Frequently Reported TEAEs (≥5.0% in Satraplatin) in SPARC

System Organ Class[a] Preferred Term	Number (%) of Patients			
	Any Grade		Grade 3/4	
	Satraplatin (N=629)	Placebo (N=313)	Satraplatin (N=629)	Placebo (N=313)
Patients with at least 1 TEAE	575 (91.4)	256 (81.8)	333 (52.9)*	93 (29.7)
Blood and lymphatic system disorders	347 (55.2)*	37 (11.8)	170 (27.0)*	12 (3.8)
Anemia NOS	151 (24.0)*	30 (9.6)	48 (7.6)*	7 (2.2)
Leukopenia NOS	60 (9.5)*	5 (1.6)	20 (3.2)*	2 (0.6)
Neutropenia	178 (28.3)*	2 (0.6)	89 (14.1)*	1 (0.3)
Thrombocytopenia	201 (32.0)*	9 (2.9)	77 (12.2)*	2 (0.6)
Gastrointestinal disorders	364 (57.9)*	88 (28.1)	49 (7.8)*	7 (2.2)
Abdominal pain NOS	33 (5.2)	10 (3.2)	2 (0.3)	1 (0.3)
Constipation	143 (22.7)*	33 (10.5)	13 (2.1)	3 (1.0)
Diarrhea NOS	150 (23.8)*	18 (5.8)	13 (2.1)*	0
Nausea	181 (28.8)*	32 (10.2)	8 (1.3)	1 (0.3)
Vomiting NOS	103 (16.4)*	27 (8.6)	10 (1.6)*	0
General disorders and administration site conditions	268 (42.6)*	102 (32.6)	48 (7.6)	20 (6.4)
Asthenia	94 (14.9)*	29 (9.3)	21 (3.3)	5 (1.6)
Fatigue	110 (17.5)*	32 (10.2)	11 (1.7)	3 (1.0)
Pyrexia	50 (7.9)	14 (4.5)	2 (0.3)	1 (0.3)
Infections and infestations	140 (22.3)*	35 (11.2)	25 (4.0)*	3 (1.0)
Urinary tract infection NOS	38 (6.0)	11 (3.5)	6 (1.0)	2 (0.6)
Investigations	164 (26.1)*	45 (14.4)	59 (9.4)*	10 (3.2)
Neutrophil count decreased	36 (5.7)*	1 (0.3)	13 (2.1)*	1 (0.3)
Platelet count decreased	52 (8.3)*	2 (0.6)	18 (2.9)*	1 (0.3)
Weight decreased	39 (6.2)	11 (3.5)	3 (0.5)	0
Musculoskeletal and connective tissue disorders	261 (41.5)	145 (46.3)	61 (9.7)	35 (11.2)
Arthralgia	73 (11.6)	43 (13.7)	8 (1.3)	6 (1.9)
Back pain	75 (11.9)	46 (14.7)	16 (2.5)	8 (2.6)
Bone pain	79 (12.6)	50 (16.0)	23 (3.7)	13 (4.2)
Metabolism and nutrition disorders	134 (21.3)*	42 (13.4)	24 (3.8)	9 (2.9)
Anorexia	76 (12.1)	25 (8.0)	4 (0.6)	2 (0.6)
Nervous system disorders	138 (21.9)	61 (19.5)	20 (3.2)	10 (3.2)
Dizziness	37 (5.9)	11 (3.5)	3 (0.5)	1 (0.3)
Headache	35 (5.6)*	8 (2.6)	2 (0.3)	0
Respiratory, thoracic and mediastinal disorders	117 (18.6)*	32 (10.2)	19 (3.0)	5 (1.6)
Cough	36 (5.7)*	5 (1.6)	0	0
Dyspnea	43 (6.8)*	9 (2.9)	6 (1.0)	3 (1.0)

[a] Multiple reports of the same preferred term for a patient are only counted once within each treatment group.

* Indicates a 2-fold and/or statistically significant greater incidence in the satraplatin group compared with placebo (p≤0.05). P-values are based on Fisher's exact test.

KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

Overall 52.9% (333/629) of patients treated with satraplatin had a Grade3/4 TEAE during the study: the majority were Grade 3 (41.8%, 263/629) and few were Grade 4 (11.1%, 70/629). The most common Grade 3 and 4 TEAEs included neutropenia (10.7% and 3.5%, respectively) thrombocytopenia (10.8% and 1.4%, respectively) and anemia (6.7% and 1%, respectively). Grade 3/4 gastrointestinal events were observed in 7.8% of patients in satraplatin and 2.2% of patients in placebo arm. Others NCI-CTC Grade 3/4 TEAEs occurred in <4% of satraplatin-treated patients. Of note, less than 1% of the satraplatin-treated patients experienced febrile neutropenia (0.6%).

Of note, an increased incidence and severity of TEAEs with increased satraplatin dose intensity has been suggested. Indeed, a greater frequency and severity of myelosuppression, gastrointestinal, hemorrhagic and infection TEAEs as well as of SAEs and of SAEs requiring new or prolonged hospitalization was observed in studies in which patients were dosed at 100-120 mg/m^2/day, compared with SPARC, in which patients were dosed at 80 mg/m^2/day. However, in several cases, determining the causality between AEs and satraplatin is made difficult by the presence of other factors contributing to the adverse events, for example the use of concomitant medications (corticosteroids, antiemetics, etc …).

Serious adverse events

In SPARC study, treatment-emergent serious adverse events (SAEs) other than death, but including SAEs temporally associated with or preceding on-study deaths, were reported for 214 (22.7%) patients, 162 (25.8%) in the satraplatin and 52 (16.6%) in the placebo group. Serious TEAEs that occurred in ≥ 1.0% of patients in the satraplatin group were anemia (2.9%), thrombocytopenia (1.9%), spinal cord compression (1.4%), and prostate cancer (1.1%). SAEs related to underlying disease comprised 19.1% (31/162) of treatment emergent SAEs reported in the satraplatin group and 26.9% (14/52) in the placebo group. Treatment-emergent SAEs assessed as study drug related by the investigator were reported for 65 (6.9%) patients, 55 (8.7%) patients in satraplatin and 10 (3.2%) in placebo group. They included anemia (1.7%) and thrombocytopenia (1.4%).

Serious TEAEs resulting in new or prolonged hospitalization were reported for 197 (21%) patients, 150 (23.8%) in the satraplatin and 47 (15.0%) in the placebo group. In general, over one half of the hospitalizations for patients receiving satraplatin were caused by myelosuppression (satraplatin: 5.2%; placebo: 1.3%), gastrointestinal disorders (satraplatin: 4.3%; placebo: 2.2%), general disorders and administration site conditions (satraplatin: 3.7%; placebo: 2.6%) and infections and infestations (satraplatin: 3.7%; placebo: 1.6%).

Of note, a significantly higher percentage of patients in the satraplatin group compared to the placebo group reported cardiovascular events and renal failure leading to new or prolonged hospitalization; however, only 9 satraplatin patients experienced cardiovascular or renal events considered by the investigator as related to study drug.

Table 12 Serious TEAEs Occurring in ≥1.0% in Satraplatin Group Requiring New or Prolonged Hospitalization in SPARC

System Organ Class[a] Preferred Term	Number (%) of Patients Satraplatin (N=629)		Placebo (N=313)	
Patients with at least 1 serious TEAE leading to new or prolonged hospitalization	150	(23.8)	47	(15.0)
Anemia NOS	21	(3.3)	3	(1.0)
Thrombocytopenia	12	(1.9)	0	
Nausea	8	(1.3)	1	(0.3)
Diarrhea NOS	7	(1.1)	0	
Dehydration	7	(1.1)	1	(0.3)
Dyspnea	7	(1.1)	1	(0.3)
Vomiting NOS	6	(1.0)	2	(0.6)
Asthenia	6	(1.0)	0	
Spinal cord compression NOS	6	(1.0)	4	(1.3)

[a] Multiple reports of the same preferred term for a patient are only counted once within each treatment group.

KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

The overall profile of SAEs in the other 28 studies conducted with satraplatin was qualitatively similar to that observed in the SPARC study. However, the overall incidence of SAEs and the incidence of SAEs requiring new or prolonged hospitalization in patients treated with satraplatin was significantly higher in Prostate Pool compared with SPARC study probably due to the higher dose of satraplatin used in these studies. Moreover, in the Prostate Pool gastrointestinal disorders were the most frequently reported SAEs that lead to discontinuation of study drug.

Deaths

In the SPARC study, as of the 15 June 2006 cut-off date, a total of 463 (48.7%) patients had died, 309 (48.7%) in the satraplatin and 154 (48.9%) in the placebo group. A total of 24 (2.5%) patients, 15 (2.4%) on satraplatin and 9 (2.9%) on placebo, died within 30 days of the last dose of study drug. The primary cause of death, as attributed by investigators, was disease progression (satraplatin: 67%; placebo: 56%). Cardiovascular disease, including cerebrovascular events, was the second leading cause of death (satraplatin: 27%; placebo: 33.3%); according to the Applicant, considering that such deaths are common in the elderly and that the incidence was similar in both treatment arms, a potential correlation with satraplatin treatment was considered unlikely.

A single death occurring on study was assessed by the investigator as possibly related to satraplatin: the patient (subject 278-11) died following a cerebrovascular accident that was experienced during administration of Cycle 2 of treatment.
Other 3 deaths that occurred more than 30 days after the last dose of satraplatin but as a result of a TEAE occurred within 30 days from drug administration were reported as drug-related. However, one death subsequent to pathological fracture (patient 416-04) was consistent with disease progression, rather than a treatment-related toxicity. Both the other two patients died as a result of renal failure; however they both had a history of renal impairment and were exposed to conditions (dehydration, contrast dye, hypotension) that may have exacerbated the pre-existing renal impairment.
In addition, two cases of adverse events that started >30 days after administration of study drug and that led to death were assessed by the investigator as study drug related. They included a patient (253-04) that experienced gastrointestinal perforation 38 days after the last dose of study drug (cycle 2), and a patient (486-06) who experienced grade 4 thrombocytopenia followed by hematuria and ischemic failure.

Laboratory findings
Hematological laboratories were among the most common abnormalities seen with satraplatin treatment. Most of the hematology nadirs occurred between days 22-28, although approximately 25% of patients had the onset of the nadir for neutrophils and platelets occurring between days 29-35.
Regarding chemistry analytes, hyperbilirubinemia and increased liver function laboratory tests were noted in satraplatin group (hyperbilirubinemia satraplatin: 10.4% vs. placebo: 3.4%) but the clinical implications of these findings are currently unknown.
Of note, the percentage of patients with a high creatinine value was similar between the satraplatin (17.0%, 102/629) and the placebo (20.9%, 62/313) groups. In the satraplatin group, 2 patients with normal baseline values had shifts to Grade 3 (0.4%, 2/549) creatinine values and both had corresponding TEAEs for renal failure: one of them died due to renal failure; he had a history of renal insufficiency.

Safety in special populations
Adverse events and laboratory values were analyzed by intrinsic (ethinicity, age, ECOG performance status and body weight) and extrinsic subgroups (food effects, study drug dose and prior use of docetaxel). No relevant differences were noted between the groups with the exception of the patients with prior use of docetaxel as first line treatment.

Safety in patients treated with docetaxel as 1st line chemotherapy
Although the Applicant states that frequencies of TEAEs overall (89.9% vs 92.9%, respectively) and of individual TEAEs were comparable between docetaxel pre-treated and not-pretreated patients, an higher incidence of fatigue (23.6% vs 11.1%, respectively), gastrointestinal AEs (62.7% vs 52.8%, respectively), hepatic toxicity (8.4% vs 3.3%, respectively) and neuropathy (6.2% vs 10.9%, respectively) was seen in patients with prior use of docetaxel. Two-fold greater frequencies in the prior docetaxel group compared with no prior docetaxel group in Grade 3/4 TEAEs were noted for the same TEAEs [fatigue (3.1% vs. 0.7%), gastrointestinal (10.2% vs. 4.9%), neuropathy (0.6% vs. 0%), and hepatic toxicity (3.1% vs. 0%)]. This is considered a relevant issue in the evaluation of the safety profile of satraplatin in the target population, considering that actually docetaxel represents the standard first line treatment registered in Europe for patients with advanced HRPC.

Hepatic impairment
In the response to the CHMP day 120 List of Questions the Applicant provided the final results of **study SAT1-04-04** evaluating the effect of hepatic impairment on satraplatin pharmacokinetics, disposition and safety. Satraplatin (80 mg/m^2/day x 5 days, q 35 days) was administered to 4 cohorts (each containing 8 patients with non-hematologic malignancies) defined by level of hepatic impairment: normal hepatic function, mild (Child Pugh Class A), moderate (Child Pugh Class B), and severe hepatic impairment (Child Pugh Class C). A trend toward decreased platinum levels in plasma and PUF was observed as hepatic function decreased.
All 32 patients (32/32, 100%) experienced at least 1 treatment-emergent AE during the course of this study. Overall, the most commonly observed AEs were nausea (14/32, 43.8%), followed by vomiting (13/32, 40.6%), anorexia and fatigue (12/32 each, 37.5%), diarrhoea (10/32, 31.3%), and oedema peripheral and thrombocytopenia (8/32 each, 25.0%). The severity of AEs varied by hepatic function group; in general, patients with greater hepatic impairment tended to experience higher severity AEs. However, the type and

severity of AEs were not unexpected given this patient population of this study and the known toxicities of the study drug. Eighteen (18) patients experienced a serious adverse event (SAE). SAEs assessed as definitely related to study drug included thrombocytopenia, neutropenia, and gastrointestinal haemorrhage.
A post-hoc analysis was performed: no evidence that impaired hepatic function led to a greater rate of generalized myelosuppression was found in this study. However, each hepatic function group included only 8 patients, a number considered to low to allow any meaningful conclusion over the safety of the drug in this subgroup of the population.
A total of 5 patients experienced TEAEs with an outcome of death: 1 in Child-Pugh Class B and 4 in Child-Pugh Class C. Two of the 5 deaths were attributed to acute renal failure assessed as possibly or probably related to study drug. The cases of renal failure occurred in the first cycle and, therefore, were considered dose-limiting toxicities (DLTs). Thus per protocol, new patients entering the study in Group 4 started treatment on a reduced satraplatin dose of 60 mg/m2/day. Three patients in Group 4 who were enrolled and treated with satraplatin prior to the 2 DLTs of renal failure did not develop renal dysfunction; one of these patients completed 8 cycles of therapy.
Considering that only 8 patients for each hepatic function group were treated with satraplatin, the safety of satraplatin in patients with hepatic impairment has not been fully established. Considering that DLTs were observed in the 1st cohort of patients receiving 80 mg/m2/day, a starting dose of 60 mg/m2/day is recommended by the Applicant, for patients with severe hepatic impairment (Child-Pugh Class C). Although the efficacy of satraplatin at this adjusted dose is not prove and not supported by pharmacokinetics data, considering the difficulties in performing such studies and the limited number of patients with severe hepatic impairment that will be considered suitable for satraplatin therapy in clinical practice, the proposal of the Applicant on this issue are considered acceptable.
In addition, patients with hepatic impairment should be monitored closely for hematological and gastrointestinal toxicity. If hematological or gastrointestinal toxicity is observed, the dose should be adjusted. Biochemical markers should be monitored for hepatic function prior to initiating each cycle of therapy. If ≥grade 3 hepatic toxicity lasting for >7 days is observed, treatment should be stopped.

Renal impairment
In the **SPARC study**, an additional analysis was performed to explore the incidence of satraplatin-induced myelosuppression in patients with baseline (calculated) creatinine clearance ≤50 mL/min (n=49; range: 28 to 50 mL/min). Although this subset of patients appeared to have more frequent and more severe myelosuppression after all cycles, when reviewed graphically, no significant correlation was found.
In the response to the CHMP day 120 List of Questions, the Applicant provided the final results of **study SAT1-04-03**, in which satraplatin (80 mg/m^2/day x 5 days q35 days) was administered to 4 cohorts (each containing 8 patients with non-hematologic cancers) defined by level of renal impairment: normal renal function (creatinine clearance >80 mL/min), mild (creatinine clearance 50-80 mL/min), moderate (creatinine clearance 30-<50 mL/min), and severe renal impairment (creatinine clearance <30 mL/min). At least 3 patients with a diagnosis of HRPC and who had progression after a first line chemotherapy were to be enrolled. The clearance of platinum after satraplatin administration appeared to be highly dependent on renal function: there was increased exposure to platinum in patients with moderate to severe renal impairment (i.e., creatinine clearance values <50 mL/min).
All 32 patients (32/32, 100.0%) experienced at least 1 TEAE. The most commonly observed AE was fatigue (20/32,62.5%), followed by nausea (18/32, 56.3%), diarrhoea (17/32, 53.1%), anorexia, (15/32, 46.9%), constipation (12/32, 37.5%), pyrexia (10/32, 31.3%), hemoglobin decreased and vomiting (9/32 each, 28.1%), anemia, dyspnea, and thrombocytopenia (8/32 each, 25.0%), dysgeusia and oedema peripheral (6/32 each, 18.8%). There were no unexpected AEs from either study drug administration or as would be expected in the patient population in this study. Patients with moderate and severe renal impairment tended to experience more fatigue, diarrhoea, vomiting, and low hemoglobin values compared with patients in the normal or mildly impaired renal function groups. Seventeen (17) patients experienced an SAE. None of these SAEs were assessed by the investigator as probably or definitely related to study drug. The following SAEs were assessed as possibly related to study drug: abdominal pain, hypotension, infection without neutropenia, and pyrexia. Four (4) patients experienced AEs with an outcome of death; 3 were in Group 2 (mild impairment) and 1 in Group 4 (severe impairment). Three (3) patients experienced disease progression that was assessed by the investigator as not related to study drug, and 1 patient experienced failure to thrive assessed as possibly related to study drug; A post-hoc analysis was also performed: no evidence that impaired glomerular filtration rate led to a greater rate of generalized myelosuppression in the patient population was found in this study. However, only 8 patients for each renal

function group were treated, a number considered to low to allow any meaningful conclusion over the safety of the drug in this subgroup of the population. Therefore, in view of the rapporteur[A3]s, the Applicant should provide a dose reduction for moderate and severe renally impaired patients, based on the continuous relationship between creatinine clearance and exposure observed in study SAT1-04-03. Moreover, patient with any grade of renal impairment should be closely monitored for hematologic and gastrointestinal toxicities.

Immunological events
Hypersensitivity reactions to platinum compounds are relatively frequent AEs observed in the clinic, occurring generally after multiple cycles of therapy. In SPARC study, 7 patients (1.1%) reported drug hypersensitivity events: 5 were considered drug-related and of them two patients had Grade 3 hypersensitivity reactions that led to discontinuation of study drug. Hypersensitivity events included edema, swelling of the tongue, vasodilatation, bright red skin, and dyspnea. In most cases they occurred after several cycles of therapy. Considering that the present Application is for oral administration of satraplatin and that the drug will be taken by the patient at home, the Pharmacovigilance Plan should closely monitor the potential risks related to this issue.

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Safety related to drug-drug interactions and other interactions
Clinical drug interaction studies of satraplatin with concomitant medications have not been conducted. However, based on the results obtained from in vitro experiments, it is unlikely that satraplatin will affect the disposition of other drugs through CYP450 or P-gp mediated mechanisms. In **SPARC** trial patients receiving concomitantly administered drugs with a significant dependency on CYP metabolism for elimination did not show significant difference in the frequency of adverse events, with the only exception of nausea. Although these results should be interpreted cautiously due to the small sample size and the retrospective nature of the analysis, pharmacokinetic interactions at these levels appear unlikely. However, when new metabolites will be characterised, the possibility for drug-drug interactions should be considered. Satraplatin-food interaction has been reported in **study SAT1-04-01**; as a consequence in the proposed SPC the Applicant recommends that patients take satraplatin on an empty stomach (see comments in section III.3, Pharmacokinetics).

Discontinuation due to AES
In SPARC study, the most frequent reason for discontinuation of study drug was disease progression (satraplatin: 63.6%; placebo: 77.1%). TEAEs that resulted in discontinuation of study drug occurred in 13.5% of patients in the satraplatin and 8.6% of patients in the placebo group. In the satraplatin group, the most common TEAEs leading to discontinuation of study drug were gastrointestinal disorders (1.7%), myelotoxicity (1.7%), spinal cord compression (1.4%) and bone pain (1.1%). A total of 6 patients (1%), discontinued study drug due to cardiac TEAEs: although the low number of patients reported the incidence was higher than in placebo group.

Pharmacovigilance System
The pharmacovigilance System has been updated and considered adequate. However, the applicant should be aware that the procedure for reconciliation between databases and data safety monitoring committees should be written and in place at the time of marketing.

Pharmacovigilance Plan
The applicant will undertake continuous monitoring for safety signals and proposes routine and enhanced pharmacovigilance practices. The risk on myelosuppression, on embryotoxic and teratogenic effects, on thromboembolic events and on gastrointestinal toxicity are covered by routine and enhanced pharmacovigilance practices and routine risk minimisation. For the other safety specifications some changes in the SPC are implemented: infections, hypersensitivity reactions, secondary malignancies, renal disorders, increase in bilirubin, infertility, adverse events such as ecchymosis and conjunctival haemorrhage, patients with renal impairment, patients with cardiac impairment, patients with underlying disease where the use of corticosteroids are not recommended.

The following topics should be closely monitored and specifically addressed in the PSURs: renal toxicity, hepatic toxicity, QTc prolongation, possible drug-drug interactions, AEs associated with platinum-containing drugs (neurotoxicity, ototoxicity, secondary malignancies), postmarketing data from patients who received previous treatment with docetaxel, postmarketing data from patients with a history of brain

metastases or of major gastrointestinal surgery or gastrointestinal pathology likely to influence absorption of oral medications, prior radiation therapy to >30% of the bone marrow or prior treatment with strontium-89, rhenium-186, or rhenium-188, and patients receiving satraplatin who had more than one prior chemotherapy regimen. In future PSUR submissions the applicant should discuss these topics in detail. Patients experiencing adverse events who have had more than one prior chemotherapy regimen should preferably also be presented in a separate table in the PSURs.

Risk Management Plan

The applicant proposes activities for risk minimisation through SPC, PL and educational material. There are patients enrolled in the SPARC study that are still receiving satraplatin. In future PSURs the MAH should ensure to discuss the progress of this study. Moreover, if any new (clinically relevant) information is revealed within this study that cannot wait for assessment by the regulatory authorities until submission date of the next PSUR, this information should be submitted immediately to the authorities with MAA's proposals for adequate measures to be undertaken.

With regard to off –label use, the applicant proposes to provide a DHPC with the SPC. This is considered not acceptable and it should be pointed out that a DHPC is a tool to communicate new information on serious risks or clinically significant changes to the SPC towards Health Care Professionals.

In addition to monitoring for off-label use and reporting on this in as much detail as possible in the PSURs, the applicant should also provide in the PSURs regular analysis of the sales data with in particular a comparison between the sales data and the projected post-authorisation usage data in view of the target population. The Applicant should provide more details on the possibility for a drug utilisation study. The applicant states that the sales effort will focus on oncologists with an additional educational focus for urologists. It is unclear what this additional educational focus for urologists entails. The applicant should clarify what is meant by this.

The potential risk for patients previously treated with docetaxel should be added to sections 1.5.2 of the RMP.

Non-clinical and clinical safety specifications

A non-clinical safety specification was identified regarding carcinogenicity. In vitro studies revealed an unequivocal carcinogenic potential of satraplatin. Also embryotoxic and teratogenic effects have been identified in rats. Identified clinical safety specifications consist of risk on myelosuppression, risk on bleeding, risk on thromboembolic events, risk on gastrointestinal toxicity, the potential risk on QTc prolongation, the potential for interactions, the potential risk on off-label use, the potential risk associated with platinum analogues, the potential risk on overdose.

Also identified was the limited information from patients with renal impairment, the lack of information from patients with hepatic impairment, the lack of information from children. Several additional safety specifications were identified by the assessor that is included in the Risk Management Plan, i.e. the identified risks on infection, on hypersensitivity reactions, on infertility, on renal toxicity and on hepatic toxicity (increased bilirubin), also the potential risk on QTc prolongation and in patients previously treated with docetaxel, and finally the lack of information from patients with cardiac impairment, lack of information from patients with a disease where the use of corticosteroids is not recommended, and lack of information from patients who had more than one prior chemotherapy regimen.

IV. BENEFIT RISK ASSESSMENT

IV.1 Introduction - Clinical context

In the European Union, prostate cancer has become a major cause of death among elderly men. In 2006, overall 301,500 cases of prostate cancer were documented in the EU and prostate cancer became the most frequently diagnosed cancer in males (24.1% of all malignancies in men and 10.4% of cancer deaths). This incidence and related mortality are increasing in many European countries, making this cancer a rapidly rising public health problem. Prostate cancer cell survival and proliferation depend primarily on the androgen receptor during early disease. The transformation of prostate cancer, which is sensitive to androgen ablative therapy, to HRPC, defined as progressive disease amidst castrate levels of testosterone, is not fully understood. Most patients become significantly disabled with reduced survival, development of significant comorbidities, diminished physical function, and most prominently, progressive bone metastases, most frequently to the spine, ribs, and pelvis.

The claimed indication of Satraplatin (Orplatna®) is the treatment of patients with metastatic hormone-refractory prostate cancer (HRPC), who have failed prior chemotherapy, in combination with prednisone or prednisolone.

IV.2 Demonstrated benefits and uncertainties

The present submission for MAA is mainly based on the SPARC pivotal study, which is a multicenter, multinational, randomized, double-blind, placebo-controlled, phase III study designated to assess the efficacy of Satraplatin plus prednisone compared with placebo plus prednisone in 2nd line therapy of HRPC. Other studies are supportive at best, because they were prematurely terminated. Relevant limitations in the study population are that only 36% of patients had substantial pain (PPI 2-5) and almost all patients (around 90%) had good ECOG performance status (≤ 1). Furthermore, as SPARC study started before the approval of docetaxel in 1st line therapy of HRPC, only 51.4 % of patients enrolled were pre-treated with docetaxel. Considering that currently docetaxel is the standard 1st line therapy in HRPC, this implies that only around one-half of the population studied fulfilled the pre-requisite for the claimed indication.

[CD4]

Co-primary endpoints of SPARC study were a composite non-validated Progression Free Survival (PFS) and Overall Survival (OS). Secondary endpoint was time-to-pain progression (TPP). Exploratory endpoints were pain and PSA response. The Applicant considered all their endpoints of clinical relevance in the target population. However, although OS can be acknowledged as acceptable endpoints, composite PFS, Time-to-Pain-Progression / pain-assessment and PSA response are not validated, and are of limited clinical relevance, respectively.

In the Applicant's response to the CHMP day 120 List of Questions final results on OS of SPARC study were provided. The analysis of the primary endpoint of progression-free survival (PFS) was not updated with the D120 responses, as the final analysis was available[A5] at the time of the original submission[CD6].

The final analysis of OS showed no superiority of Satraplatin over placebo: median OS was 61.3 weeks in Satraplatin group compared with 61.4 weeks in placebo group (Log-rank p-value: 0.799; HR=0.97; 95% CI: 0.83, 1.13). This finding is of importance, considering that OS was the co-primary endpoint of the study and represents an objective parameter in the evaluation of clinical benefit. As the OS analysis failed to show a significant benefit of Satraplatin over placebo, evaluation of validity and robustness of the composite PFS results become crucial in the evaluation of efficacy of Satraplatin in the target population.

PFS was defined as a composite endpoint composed of tumor progression, progression related to skeletal events and symptomatic progression, or death. Although some of the individual components of this definition of PFS have been used in other phase III registration studies, this definition of PFS has not been previously employed in a registration trial and lacks validation. Whether the composite PFS endpoint used in SPARC study can be considered a surrogate endpoint to assess clinical benefit in the target population has not been demonstrated yet. Some components of this composite definition may be subject to significant investigator's bias, and this is particularly relevant because the adverse events expected with Satraplatin

may have compromised the double-blind design of the study. Moreover, the evaluation of the analgesic score and subsequent symptomatic progression (as part of composite PFS) is biased, because SPARC study protocol did not provide a planned pain management and because only narcotic analgesics were counted, whereas it is recognized that the use of narcotic analgesics varies widely between different countries. Indeed, the justifications of concerns related to these issues provided by the Applicant are unsatisfactory.

The analysis on composite PFS for the ITT population (as adjudicated by the IRC), showed a statistically significant difference between the progression free survival curves ($p<0.001$ at log-rank test) with a significant 33% reduction in risk of progression for Satraplatin compared with placebo (HR=0.67, 95% CI: 0.57, 0.77, $p<0.001$). However, the difference in median composite PFS between the two arms was only 9.8 days, which must be considered not clinically relevant (median composite PFS Satraplatin: 11.1 weeks, placebo: 9.7 weeks).
Looking at the Kaplan-Meier curves, the difference between Satraplatin and placebo curves becomes mostly apparent after two courses (~ 10 weeks) of therapy: this time span corresponds with the official first re-evaluation by imaging after randomization and, of note, at that time around one-half of the patients already had progressed. This fact contributes to another potential bias in the trial evaluation and indicates that, if there is a benefit of Satraplatin on PFS, it is little and only apparent in a small part, and possibly distinct, population studied. However a subpopulation that may potentially benefit from Satraplatin treatment has not been identified by the Applicant. Another consequence of the fact that half the patients already had progressed at the time of first evaluation, is that single summary statistics describing an "overall treatment benefit" such as the mean and the hazard ratio, and the log-rank test cannot lead to a reliable interpretation, because their magnitude is mainly driven by the difference in PFS distributions after 10 weeks.

Moreover, a low concordance level between the investigators and the IRC (independent review committee) in the assessment of radiographic progression (less than 70%) was reported, indicating only limited reliability of this important outcome parameter. Even considering critical assessments (by IRC or investigators) the benefits showed very modest (PFS) and therefore of no clinical relevance.
Sensitivity analyses performed by the Applicant to support the PFS results did not resolve the major concerns about the claimed clinical relevance of the difference between the treatment arms and the validity of the composite PFS.

In the evaluation of secondary and other endpoints, TPP and pain response rate were reported as significantly higher in Satraplatin (53 weeks and 25.4%, respectively) compared with placebo group (36.6 weeks and 12.4% respectively); a 36% reduction in the risk of pain progression associated with Satraplatin therapy was observed (HR: 0.64, CI: 0.51,0.79; $p<0.001$).
However, the secondary and the other endpoints are exploratory and can not be considered supportive for a marketing claim because in the final analysis plan (version 2 dated March 2006) there was no pre-specified plan for adjustment for multiplicity or ordering of secondary endpoints. In fact, only a portion (35-55%) of patients enrolled were eligible for evaluation for any one of these secondary endpoints. Finally, the results of endpoints related to pain response and time to pain progression are basically biased by the above mentioned concerns on the evaluation of the analgesic score.

IV.3 Demonstrated risks and uncertainties

Overall, the safety profile of Satraplatin was consistent across studies and was typical for an orally administered and cytotoxic platinum drug with more similarities with carboplatin than cisplatin: haematologic and gastrointestinal toxicities were prominent and dose limiting, whereas nephrotoxicity, ototoxicity and neurotoxicity were limited.
The most commonly reported adverse events were haematological and gastrointestinal events; fatigue, asthenia, infections and hemorrhagic/thrombotic events were also reported as drug related. An increased incidence and severity of TEAEs with increased Satraplatin dose intensity has been suggested, considering that a greater frequency and severity of myelosuppression, gastrointestinal, hemorrhagic and infection TEAEs as well as of SAEs and of SAEs requiring new or prolonged hospitalization, was observed in studies in which patients were dosed at 100-120 mg/m^2/day, compared with SPARC, in which patients were dosed at 80 mg/m^2/day.

Myelosuppression (i.e. thrombocytopenia, neutropenia and anaemia) was experienced by 60.4% of patients treated with Satraplatin and 14.4% of patients treated with placebo in SPARC study and represented the most frequent AEs resulting in drug discontinuation, dose reduction and cycle delay. In SPARC study, an increased red blood cells and platelet transfusions occurred in Satraplatin compared with placebo treated patients.
Gastrointestinal toxicity was common (57.9% of patients treated with Satraplatin and 28.1% of patients treated with placebo in SPARC study) but considered manageable and reversible: nausea (28.8%), diarrhoea (23.8%), constipation (22.7%) and vomiting (16.4%) were the most frequently reported, but generally they were of mild or moderate severity at the dose used in SPARC: Grade 3 events occurred in 7.8% of patients treated with Satraplatin and no Grade 4 gastrointestinal AEs have been reported. Overall gastrointestinal events accounted about 4.3% of SAEs requiring new or prolonged hospitalization.
The incidence of renal failure was limited (1.4% in SPARC study) but serious adverse events and deaths related to renal failure were reported as study-drug related. Final results of study SAT1-04-03 evaluating pharmacokinetics and safety of Satraplatin in patients with various degrees of renal impairment showed an increase in platinum exposure in renally impaired patients with a continuous relationship between creatinine clearance and platinum exposure. On this basis a Satraplatin dose reduction for patients with moderate and severe renal impairment is considered necessary and indications over such dose adjustments should be provided by the Applicant.

In Satraplatin treated patients increase in bilirubin and liver function laboratory tests have been frequently observed, although the clinical implication of this finding is currently unknown. Final results of study SAT1-04-04 evaluating pharmacokinetics and safety of Satraplatin in patients with various degrees of hepatic impairment have been provided by the Applicant. Considering that 2 deaths due to renal failure probably related to study drug have been observed in patients with severe hepatic impairment (Child-Pugh C), the dose reduction proposed by the Applicant (from 80 mg/m2 to 60 mg/m2) is agreed and, based on the observation that platinum levels appear to decrease as hepatic function decrease, no further recommendation with regard to dosing of hepatically impaired patients is considered necessary.

Episodes of hypersensitivity, neurological events and toxicity were rare and of mild or moderate severity but, due to the relatively small number of patients treated with Satraplatin, the potential of these Satraplatin-related events need to be further assessed within the pharmacovigilance plan.

Moreover, the additional safety concern for the subgroup of the SPARC study population who had received docetaxel-based regimen as 1st line treatment is still not solved. Indeed, in docetaxel pre-treated patients receiving Satraplatin a significantly increased incidence of grade 3/4 gastrointestinal and hepatic adverse events, fatigue, anorexia, infections, hypersensitivity reactions and neuropathy was observed compared with patients receiving Satraplatin and not pre-treated with docetaxel.

Finally, in SPARC study patients were selected on the basis of a good performance status and lack of significant hepatic or renal co-morbidities, e.g. patients with brain metastases, diseases where corticosteroids are contraindicated, prior radiation therapy to > 30% of the bone marrow or prior treatment with strontium-89, rhenium-186 or rhenium-188.
As the "true" patient population with advanced docetaxel refractory prostate cancer is not properly represented in the pivotal SPARC study, the safety profile of Satraplatin as presented must be considered too favourable. This issue may be to some extent solved in the Risk Management Plan.

IV.4 Balance

In general, as outlined by EMEA guidelines (CPMP/EWP.205/95/Rev.3), the goals of therapy for 2nd line treatments in HPRC should be the same as for 1st line, and include primarily extending survival, slowing the disease progression and reduce related-complications. Moreover, in 2nd line patients where the life expectancy is poor, the impact of new therapies on the quality of life should be considered in the evaluation of the clinical benefit.
From a regulatory perspective, the exceptional event of a submission with only one pivotal study is acceptable by EMEA, but as outlined by the EMEA guidelines, "licensing based on one pivotal study, requires demonstration of efficacy at levels beyond standard criteria for statistical significance" (CPMP/EWP.205/95/Rev.3; CHMP/EWP/2330/99). Moreover, the same guideline

(CPMP/EWP.205/95/Rev.3) assesses that "if there are no evidence based next line therapies available and if the period of time from disease progression to death is expected to be short, Overall Survival (OS) is considered to be the most appropriate endpoint…". The final updated OS results provided by the Applicant did not show a significant benefit of Satraplatin over placebo in the target population.
In the analysis of the composite and non-validated PFS there are major concerns about the validity of the composite PFS used in SPARC study and the claimed clinical relevance of the results: the difference in median PFS between the two study arms (9.8 days) was not statistically significant and not clinically relevant, suggesting a lack of benefit of Satraplatin at least for the majority of the population.
From a patient and a medical perspective, when no survival neither slowing disease progression is clearly expected from a new treatment, quality of life and reduction of disease related symptoms become important treatment goals. In SPARC study the balance between benefit in terms of quality of life and risks related to therapy is not clear, because quality of life has not been formally evaluated and the evaluation of pain progression and pain response is biased by the methods used in the assessments because pain management was not pre-planned and the use of analgesic non-narcotics was not considered. Moreover, the increase in several grade 3/4 adverse events observed in the subgroup of the population that received docetaxel as 1st line chemotherapy (which represents the actual target population for the indication claimed), as well the absence of detailed data regarding the impact of Satraplatin in terms of quality of life make it difficult to evaluate the real impact of Satraplatin on the quality of life of the target population.

IV.5 Conclusions

Overall the benefit/risk ratio is considered negative. Satraplatin failed to show a clinically relevant and convincing benefit in terms of OS and PFS in the target population in comparison with a placebo as comparator in the pivotal phase 3, randomized, controlled, double-blind SPARC study. Moreover, major concerns about the validity of the composite PFS endpoint as employed in this study still remain.