20 January 2011
EMA/CHMP/66633/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report
For
Jevtana
(cabazitaxel)

Procedure No.: EMEA/H/C/002018

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

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List of abbreviations

AEs	Adverse events
ALK	Alkaline phosphatase
AS	Analgesic score
AUC	Area under the curve
BLQ	plasma concentration below the limit of quantitation
BM	Bone metastasis
BMI	Body Mass Index
BSA	Body surface area
CBZ	Cabazitaxel
CL	Clearance
CR / PR	Complete response / partial response
CT	Computed tomography
DoE	Design of Experiment
ECG	Electrocardiography
ECOG PS	Eastern Cooperative Oncology Group performance status
EU	European Union
GALT	gut-associated lymphoid tissue
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practices
HCPC or mHRPC	Hormone-resistant prostate cancer or metastatic hormonoe-resistant prostate cancer
HDL	High-density lipoprotein
hERG	Human ether-a-go-go related gene
HNSTD:	Highest non severely toxic dose
HPLC	High Performance Liquid Chromatography
HR	Hazard ratio
IDMC	Independent data monitoring committee
IPC	in-process controls
ITT	Intent to treat
LDL	Low-density lipoprotein
LH-RH	luteinizing hormone-releasing hormone
LM	Liver metastasis
MBC	Metastatic breast cancer
mdr-1	multidrug resistance gene
MRI	Magnetic resonance imagery
MTX	Mitoxantrone
NOAEL:	No-observable adverse effect level
NOEL:	No observable effect level
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PP	Per protocol
PPI	Present pain intensity
PSA	Prostate specific antigen
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of product characteristics
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TP	Tumour progression
TT	Tumour type
TTP	Time to tumour progression
VLDL	Very low-density lipoprotein

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi-aventis submitted on 20 April 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Jevtana, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 October 2009.

The applicant applied for the following indication:

Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/146/2009 for the following conditions:

- treatment of prostate carcinoma

on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 19 March 2009. The Scientific Advice pertained to quality aspects of the dossier.

Licensing status

Jevtana (cabazitaxel) has been given a Marketing Authorisation in the United States of America on 17 June 2010.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pierre Demolis (FR)**	Co-Rapporteur: **Robert James Hemmings (UK)**

- The application was received by the EMA on 20 April 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2010.
- During the meeting on 23 September 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 November 2010.
- During the CHMP meeting on 16 December 2010 the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 December 2010.
- The Rapporteurs circulated an Updated Joint Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 7 January 2011.
- During the meeting of January 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Jevtana on 20 January 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 January 2011.

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2. Scientific discussion

2.1. Introduction

Prostate cancer is a major worldwide health problem and is the most frequently diagnosed male malignancy, with 301,500 cases of prostate cancer documented in 2006 in the EU.

Initial treatment

The initial treatment for metastatic adenocarcinoma of the prostate consists of androgen ablation, either surgically with bilateral orchiectomy, or medically with luteinizing hormone-releasing hormone (LH-RH) receptor agonists. At this stage, further hormonal manipulations such as treatment with antiandrogens, and subsequent antiandrogen withdrawal can be associated with responses of short duration but without improvement in survival duration.

Patients with metastatic hormone-resistant prostate cancer (mHRPC)

Treatment options for patients with hormone-refractory disease remain limited and include palliation of symptoms (especially pain) and/or systemic cytotoxic chemotherapy. Prior to the approval of Taxotere in 2004, cytotoxic chemotherapy was not routinely administered to patients with hormone refractory metastatic prostate cancer (HRPC). The therapeutic options and clinical treatment for such patients were limited to cyclophosphamide, anthracyclines and anthracycline types (doxorubicin and mitoxantrone), and estramustine (combination alkylating agent and hormone). Single agent chemotherapy has been associated with palliative effects but no single agent has been associated with an objective response rate greater than 30%. Combinations of cytotoxic agents have been investigated with evidence of enhanced activity in terms of palliation and prostate specific antigen (PSA) decline but the safety profile of these combinations remains a limitation, especially in elderly men with concurrent medical problems and limited bone marrow reserve. Although the role for chemotherapy in symptom palliation and PSA response was well established, the efficacy of these regimens was relatively modest and no survival advantage had been demonstrated with any of the treatments. Based on results from two Phase 3 trials, the combination of mitoxantrone with corticosteroids was established as the reference treatment in metastatic HRPC. Taxotere in combination with prednisone was approved in 2004 for the treatment of androgen independent metastatic prostate cancer patients. A combination of docetaxel and estramustine was associated with a clinical benefit in terms of overall survival, time to tumour progression (TTP), and 50% decline in PSA, compared with mitoxantrone-treated patients.

Patients with mHRPC previously treated with a docetaxel-containing regimen

The standard of treatment for patients with mHRPC who progress following Taxotere as standard first line therapy is evolving, with no therapy approved for treatment of such patients. Palliative effects with respect to pain control have been observed in HRPC patients following the administration of either corticosteroid alone [Tannock I et al (1989) J Clin Oncol &(5):590-7] or mitoxantrone administered with either prednisone or hydrocortisone [Osoba D et al (1999) J Clin Oncol 17(6): 1654-63, Kantoff PW et al (1999) J CLin Oncol 17(8): 2506-13]. Supportive care, with various non-approved agents with limited activity, is currently used in this setting, palliation being the main goal of therapy [et al (2010) Cancer Treat Rev 36(6):501-6]. Finally, several new investigational agents are being tested in patients who progress during or after receiving a Taxotere-based regimen in the first line setting.

About the product

Cabazitaxel is a semi-synthetic derivative of the 10-deacetyl Baccatin III, which is extracted typically from European yew needles, that promotes tubulin assembly in vitro and stabilises microtubules against cold-induced depolymerization.

The indication applied for initially and finally approved was the following:

Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

2.2. Quality aspects

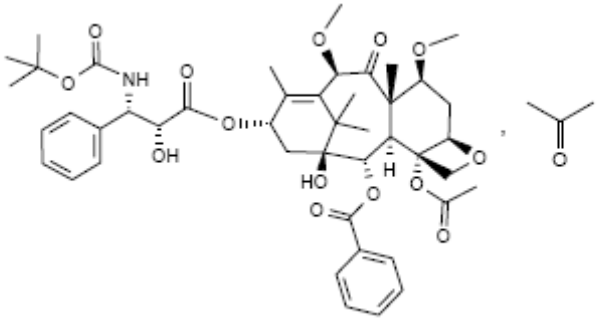
The Applicant requested scientific advice for cabazitaxel in January 2009 pursuant to Article 57(1)(n) of Council Regulation No (EC) 726/2004. During the plenary meeting held on 16-19 March 2009, the CHMP adopted the co-ordinators' report and agreed on the advice to be given to the Company. (EMEA/H/SAWP/137528/2009). All questions were on drug product.

2.2.1. Introduction

The drug substance is cabazitaxel acetone solvate. Cabazitaxel is the 7,10-dimethoxy analogue of docetaxel. Cabazitaxel (Jevtana) is a new member of the Taxane family. Other compounds in this group include docetaxel and paclitaxel. Many of these low-aqueous solubility compounds can be solubilised for intravenous infusion by using a combination of alcohols and non-ionic surfactants, in this particular case ethanol and polysorbate 80.
The product is supplied as a sterile non-aqueous concentrate for solution for infusion containing cabazitaxel 60mg/1.5ml packaged in a glass vial, and an additional solvent for dilution of the Concentrate The Solvent is a sterile, non pyrogenic 13% w/w aqueous solution of ethanol. The solvent is a clear colourless liquid and is packaged in a glass vial. The concentrate and the solvent are intended for the preparation of a premix solution of cabazitaxel at 10mg/ml prior to dilution with 0.9% saline or 5% dextrose solution in an infusion bag.

2.2.2. Active Substance

The INN name of the active substance as base is cabazitaxel. The chemical name is (2α,5β,7β,10β,13α)-4-(acetyloxy)-13-({(2R,3S)3-[(tertbutoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo 5, 20-epoxytax-11-en-2-yl benzoate-propan-2-one (1:1). The molecular formula of active substance is C45H57NO14. C3H6O its relative molecular mass 894.01 (acetone solvate), 835.93 (solvent free) and its structural formula is shown below.



Cabazitaxel is a white to almost white non hygroscopic crystalline powder, practically insoluble in water. Cabazitaxel acetone solvate contains 11 asymmetric centers. The specific stereochemistry is fixed for each centre as shown in above structure. Its logP is 3.88 ± 0.03, at 24°C, pH 7 in presence of 0.15 M KCl.
Cabazitaxel shows polymorphism. Acetone solvate (Form A) was selected on basis of manufacturing feasibility, reproducibility, and of stability.

Manufacture

The manufacturing process of cabazitaxel comprises a number of steps that yields the desired polymorph. If required, reprocessing of any intermediate or drug substance batch is foreseen in accordance with ICH Q7A guideline by repeating all or part of the related process step.

Sufficient information has been presented regarding the critical steps and intermediates, including in-process controls (IPC).

Specification

The drug substance specification includes tests for appearance (visual), appearance of solution (Ph Eur), identification (IR, HPLC), specific optical rotation (Ph Eur), assay (HPLC), related substances (HPLC), sulphated ash (Ph Eur), heavy metals (Ph Eur), bacterial endotoxins (Ph Eur), water content (Ph Eur), microbial contamination (Ph Eur), residual solvents (GC) and acetone content (GC).
Only one reagent used in the synthesis of cabazitaxel is considered potentially genotoxic. A TTC value of 20 µg /day (based on the intended cabazitaxel dose in human (25 mg/m^2 *i.e.* ~ 40 mg/day)), corresponds to a limit of 500 ppm in cabazitaxel acetone solvate. Results of 6 batches shows that the levels of the genotoxic material determined using a validated GC method are consistently well below the calculated TTC value and routine determination is therefore not deemed necessary.
Results from more than 10 batches, three of which commercial scale, have been presented, showing that the production process together with the specifications set at the different stages upstream in the synthesis allow the manufacture of drug substance batches complying with the specification proposed.

Stability

Stability data are presented for three full-scale representative batches for which 12-month data under long-term conditions (5°C) and 6-month data under accelerated conditions (25°C/60%RH) are available.
Supportive stability data on one full-scale batch for which 36-month data under long-term conditions and 6-month data under accelerated conditions were also presented.
All data are well within the proposed specification. No significant change has been observed for any of the parameters tested.
Stress stability testing allowed the determination of degradation pathways and appropriateness of analytical procedures for stability.
Photo-stability study was conducted on one primary stability batch according to ICH Q1B. Cabazitaxel acetone solvate is slightly photosensitive, when exposed to intense light. However no special precaution of storage to light is added, because the substance is stored under refrigerated conditions and is packaged in suitable package.
Based on the stability data provided a re-test period of 24 months when stored between 2-8°C in the proposed container is proposed.
In accordance with EU good manufacturing practices (GMP) guidelines [1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The proposed medicinal product is a concentrate for solution for infusion at 60 mg/1.5 ml, supplied with a solvent vial containing 4.5 ml of a 13% w/w aqueous solution of ethanol (96 per cent) for the preparation of an intermediate premix at 10 mg/ml, prior to dilution with 0.9 % sodium chloride solution or 5 % dextrose solution in an infusion bag. The product is a micellar formulation intended for intravenous use only.

The use of cabazitaxel Form A was justified on the basis that the product is a parenteral concentrate and any potential physico-chemical impact of the choice of initial solid form would not be critical.
The formulation of cabazitaxel concentrate for solution for infusion was established taking into account prior in-house knowledge from development of other taxoid parenteral products (Taxotere-docetaxel), which met the same intended target product profile.
The provided information is supportive enough to consider acceptable the transposition of the formulation marketed with docetaxel to the new entity cabazitaxel, without further optimization. Like

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docetaxel (Taxotere), cabazitaxel has poor aqueous solubility (8µg/ml) and surfactants such as polysorbate 80 are required to solubilise it. Because it is difficult to achieve homogeneity by direct mixing of a polysorbate solution with water, a concentrate is supplied with an aqueous solvent containing 13%w/w ethanol to allow the preparation of a premix at 10 mg/ml which could then be diluted in infusion medium prior to administration.
Upon dilution in water, surfactants such as polysorbate 80 are known to extemporaneously spontaneously form, above a certain concentration, micellar solutions that increase solubility of poor soluble drugs, like cabazitaxel acetone solvate, in an aqueous environment. The optimum pH for satisfactory stability of cabazitaxel concentrate has been defined conducting a study using polysorbate 80 at various pHs.
Stability of the micellar system in infusion solutions has been studied. It has been demonstrated that the micellar system is capable of ensuring chemical and physical stability of the formulation in the recommended conditions for use as per the SmPC.
Based on the above, it can be considered that cabazitaxel is almost totally micelle-solubilised for infusion solutions. A safety margin is kept though by reducing the recommended maximum storage durations at the different temperatures.
Extensive experimentation has been carried out to assess the risk of drug precipitation resulting from super saturation. Results presented ensure that crystallization is avoided by application of the appropriate instructions of the SmPC.

Chemical and physical compatibility studies were conducted on cabazitaxel infusion solutions prepared at a concentration ranging between 0.10 and 0.26 mg/ml with 0.9% NaCl or 5% dextrose in different infusion containers and the use of PVC/DEHP bags and of polyurethane sets have been excluded. Stability was demonstrated for 48 hours under refrigerated conditions. As an added precaution to ensure there is no risk of crystallization, the recommendations for storage of the infusion solutions at ambient temperatures will be limited to 8 hours.
The sterile finished product is intended for single-use only and meets the Pharmacopoeia requirements for sterility and bacterial endotoxins.
An in-use study mimicking infusion conditions showed that the micellar system is stable from start to end of infusion and is not perturbed by the use of filter.

Ethanol is also used as co-solvent in the solvent for dilution accompanying the drug product. Compatibility of the excipients with cabazitaxel acetone solvate is demonstrated from stability studies. The solvent for dilution is identical in qualitative composition and concentration of ethanol as used in the dilution of the already marketed Taxotere
The ethanol aqueous solvent for dilution qualitative and quantitative composition is the same as for Taxotere.

Overfills of the concentrate vial and of the solvent vial were proposed to ensure a premix solution of 10 mg/ml and a nominal volume of 6ml can be withdrawn from the premix vial for dilution in infusion bag.

Closure integrity testing was performed. All test vials and negative controls were found to be negative for microbial growth and all positive controls were found to be positive for microbial growth respectively which demonstrated the integrity of the container closure.
The packaging components for the solvent are the same as the ones for the drug product vial (concentrate) and the same as the ones used for accompanying solvent for dilution for the currently marketed Taxotere.

Manufacturing process development was based on the manufacturing process of Taxotere. A documented justification for not choosing terminal sterilization as the method for sterilization is provided. Sterilizing filtration is thus applied. The sterilizing filters used have been validated for microbial retention efficacy, integrity and compatibility. The suitability of filters was also demonstrated by suitable method. As far as the solvent is concerned it is terminally sterilised.

Closure integrity for both the concentrate and the solvent has been validated through microbial ingress test.

Adventitious agents

Not applicable. No materials of animal or human origin are used in the manufacturing of cabazitaxel, concentrate for solution for infusion, neither for the solvent for dilution for cabazitaxel.

Manufacture of the product

The manufacturing process for the solvent has been well described. Satisfactory process validation data are presented for three batches. All data are with the proposed specification.

The manufacturing process for the concentrate has been well described. Process validation data were presented for five full scale batches and showed that tested parameters were within specification. The holding times were also defined. Satisfactory media fill and filter integrity studies were presented ans no contaminated vials were observed. Based on the provided information the aseptic process is considered validated.

Product specification

The release and shelf-life specifications of the solvent include tests and limits for appearance (visual), clarity and degree of coloration (Ph Eur), identification (Ph Eur), ethanol content (Ph Eur and GC), particulate contamination (Ph Eur), uniformity of dosage units (Ph Eur), sterility (Ph Eur) and bacterial endotoxins (Ph Eur).
Batch data for four batches were provided. All data are within the proposed specification.

The release and shelf-life specifications of the concentrate include tests and limits for appearance and colour (visual), appearance of solution S (Ph Eur), identification (HPLC, TLC), assay (HPLC), degradation products (HPLC), pH (Ph Eur), water content (Ph Eur), particulate contamination (Ph Eur), uniformity of dosage units (Ph Eur), sterility (Ph Eur) and bacterial endotoxins (Ph Eur).
Batch data were presented for four batches. All data are within the proposed specification.

Stability of the product

For the solvent, stability studies are presented for three batches stored under long term conditions at 5°C, 25°C/60%RH and 30°C/65%RH up to 12 months and under accelerated conditions at 40°C/75%RH up to 6 months only. All tested parameters are within the proposed specification.

Supportive stability data are presented for the solvent for dilution used in conjunction with the currently marketed Taxotere is identical to the proposed solvent for dilution up to 36 months for three commercial scale batches stored under long term and accelerated conditions. All data are within the proposed specification.

Results from photostability studies carried out in line with ICH guidelines show that the product is not affected by light.

Based on the stability data provided the proposed shelf-life when stored in the proposed container is considered acceptable for the solvent.

For the concentrate, stability studies were undertaken from full scale three batches manufactured with the proposed process under ICH long-term, intermediate and accelerated conditions (i.e. 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH). Results are available for up to 12 months of storage at 5°C and 25°C, up to 18 months at 30°C and up to 6 months at 40°C. The samples are packaged in that identical to the commercial one. For each condition vials were stored inverted in order to assess any product interaction/degradation with the stopper during long term storage.

One batch among primary stability batches was subjected to photostability according to ICH guideline. Results showed that the product is not sensitive to when packaged in the proposed primary packaging system.

A freeze/thaw cycling study was also conducted. All data were within the proposed specification.

Results showed no significant change in any of the parameters tested had been observed after 6 months of storage under accelerated condition (40°C/75% RH). No significant change in any of the parameters tested had been observed after 18 months of storage under long-term condition (30°C/65% RH). Since a significant change was observed upon storage at 5 ± 3°C, the additional label "Do not refrigerate" was added.
Based on the overall physico-chemical data generated during the compatibility/in-use studies, it is recommended:
- not to use PVC bags and polyurethane infusion sets for cabazitaxel infusion solutions,

- to limit storage to 8 hours at ambient temperature, including 1-hour intravenous infusion,
- to limit storage to 48 hours under refrigerated conditions,
- to use an in-line filter of 0.22 micrometer nominal pore size during administration.

Cabazitaxel solution for infusion can be infused over 1 hour at ambient temperature and under normal lighting conditions.

According to the results obtained the shelf-life period and storage conditions are accepted.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion and Conclusion on chemical, pharmaceutical and biological aspects

The quality of Jevtana concentrate and solvent for solution for infusion is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. At the time of the CHMP opinion, there were two quality issues that will be resolved as Follow-up Measures within an agreed timeframe. However, none of them is expected to have a negative impact on the Benefit Risk balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

Cabazitaxel (also known as XRP6258, RPR116258A) is a semi synthetic derivative from 10-deacetyl Baccatin III, which is extracted typically from European yew needles.
Primary pharmacology studies were conducted in mice and safety pharmacology studies in mice, rats, rabbits and dogs. Pharmacokinetics and toxicology studies were primarily conducted in mice, rats and dogs. Certain pharmacokinetic studies were also conducted in rabbits and monkeys. With the exception of the local tolerance in rabbits, all *in vivo* studies submitted used the intravenous route, similarly to the clinical route of administration.
Single- and repeated-dose toxicity studies as well as genotoxicity, reproductive toxicity, haemocompatibility and local tolerance toxicity studies were performed in accordance with Good Laboratory Practices (GLP) regulations. All GLP studies were conducted using fully characterised batches of drug substances that were representative of the clinical and/or commercial product in terms of impurity content, including genotoxic impurities. All studies in primary pharmacology, in pharmacokinetic studies and in toxicology conducted to determine doses for subsequent studies were performed according to internal Standard Operating Procedures (SOP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Applicant has provided numerous *in vitro* and *in vivo* studies investigating the antitumour activity of Cabazitaxel in several tumour cell lines and various cancer models sensitive or resistant to docetaxel. However, data related to the proposed therapeutic indication are very limited.

In vitro, Cabazitaxel demonstrated anti-tumour activity in sensitive murine and human cell lines. Cabazitaxel showed a cytotoxic activity similar to docetaxel (IC_{50} values post 4 days exposure ranging

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from 0,004 to 0,035 µmol/L, corresponding to 3 to 29 ng/mL). For docetaxel, IC_{50} values ranged from 0.0077 to 0.061 µmol/L (6.2 to 49 ng/mL).

Moreover, as docetaxel was found to be a metabolite of Cabazitaxel, the *in vitro* activity of the 2 precursors of docetaxel, RPR123142 (10-O-demethyl-cabazitaxel) and RPR 112698(7-O-demethyl-Cabazitaxel), were also tested against the P388 cell line after 4 days of continuous exposure.
The two metabolites showed cytotoxic activity with comparable IC_{50} values with regard to cabazitaxel using the same cell line.

In vitro, Cabazitaxel demonstrated activity in several murine and human resistant cell lines. The selected cell lines included cell lines expressing the multidrug resistance gene (mdr-1) and tumour cell lines resistant to selected chemotherapeutic agents. However, no docetaxel-resistant prostate tumour cell line was tested for cross resistance to Cabazitaxel.

Cabazitaxel was evaluated by the IV route using different intermittent schedules. It demonstrated activity against several human tumours xenografted in mice including advanced cancers. Regarding prostate cancer, only one study is available investigating the activity of Cabazitaxel against advanced stage SC DU 145 (a human prostate adenocarcinoma) on Swiss nude female mice.
The schedule dependency was investigated using non tumour-bearing mice and mice bearing early mammary adenocarcinoma. According to *in vivo* data, Cabazitaxel showed a trend for schedule dependency with maximum tolerated dosages 2.4- and 4.8-fold higher with a daily (day 1 to 5) and an intermittent (day 1 and 5) schedule, respectively, than with a split-dose schedule (day 1 to 5, 3 times a day).

Secondary pharmacodynamic studies

The affinity of Cabazitaxel on receptor binding sites was evaluated on binding sites involved in the regulation of numerous physiological functions. These included classical neurotransmitters, labelled binding sites on protein involved in uptake processes and in some central nervous system regulatory processes.
Labelled binding sites present in 2 ion channels (verapamil-sensitive Ca^{++}, tetrodotoxin-sensitive Na^{+} and batrachotoxin-sensitive Na^{+}) were also studied.
Cabazitaxel was ineffective in displacing the 25 studied radioligands from their specific binding sites whatever the concentration tested.

Safety pharmacology programme

No physiologically relevant effects were noted in the central nervous, respiratory and gastrointestinal systems after IV administration of cabazitaxel (from 0.5 to 5 mg/kg corresponding to 3 to 30 mg/m^2) in rats and no interactions with various spasmogens were observed in vitro in guinea-pig ileum preparations up to 10 µmol/L (8360 ng/mL).
Some increase in urinary K+ and Cl- concentrations were observed in rats at 1.5 mg/kg (9 mg/m^2) during the 0-3 hours measurement period and decrease in urinary K+ was observed at 1.5 and 5 mg/kg (corresponding to 9 and 30 mg/m^2) during the 6-24 hours measurement period. No specific findings on the renal system were observed in rats in other toxicity studies.

Cabazitaxel was devoid of effect on human ether-a-go-go related gene (hERG) currents up to 30 µmol/L (corresponding to 26 821 ng/mL, limit of solubility) and did not modify the action potential parameters of sheep Purkinje fiber in vitro preparations at up to 10 µmol/L (8360 ng/mL). The concentration of 26 821 ng/mL corresponded to approximately 50-fold the maximum concentration (C_{max}) of cabazitaxel achieved in human patients receiving the therapeutic dose of 25 mg/m^2.
Furthermore, cabazitaxel infused over approximately 1 hour at 0.45 mg/kg (9 mg/m^2) in anesthetised dogs produced similar cardiovascular and hemodynamic changes (decrease in arterial blood pressure, left ventricular systolic pressure, left ventricular dp/dtP-1, cardiac output, stroke volume and occasional increase in RR interval, QT and QTc, decrease in PR interval) to those noted after the administration of the vehicle alone (PS80/ethanol/5% glucose) and were therefore likely attributable to the PS80 component of the vehicle (non specific histamine releaser in dogs).

Due to the very poor solubility of cabazitaxel, it was not possible to use an inactive solvent to avoid PS80 effects. No specific study with conscious telemetered dogs were considered necessary with cabazitaxel as electrocardiography (ECG) evaluations have been performed in the 13-cycle intravenous toxicity study in non anesthetised dogs up to 0.5 mg/kg/adm (10 mg/m2/adm) and no compound-

related effects were observed on any parameters. However increases in heart rate values associated with decreases in PR interval values (as compared to the respective pre-test values) were noted in all groups at the end of infusion on each dosing cycle. These changes were considered related to the PS80 content in the vehicle administered since heart rate and PR interval values were altered to the same extent in control and cabazitaxel-treated dogs. Heart rate and PR interval duration were no longer modified (as compared to the respective pre-test values) when measured 24 hours after dosing, at any dosing cycle and dose level. Consequently, in pre-clinical studies, cabazitaxel did not produce by itself cardiovascular effects and the applicant states that no cardiovascular effects have been reported in human in the different clinical trials.

Pharmacodynamic drug interactions

No formal drug interactions studies were carried out.

2.3.3. Pharmacokinetics

Pharmacokinetics studies were performed in mice, rats and dogs. After single or repeated administration, Cabazitaxel plasma exposures increased with dose and no plasma accumulation was observed in all species.
No gender effect was observed except in one study (single-dose toxicity study in dogs) at the highest dose.

Methods

Studies were conducted using [14C]-cabazitaxel with a radiochemical purity above 97.5%, which is suitable for the purpose of these studies. The isotope labelling was biologically stable.
Concentrations were measured by liquid scintillation counting for radioactivity in biological samples, and/or by autoradioluminography for radioactivity in tissues and/or by High Performance Liquid Chromatography (HPLC) with mass spectrometric detection or radiometric detection for the parent drug and its metabolites. The bioanalytical assay methods fulfilled the requirements in terms of specificity, reproducibility, repeatability, accuracy and precision to carry out pharmacokinetic and toxicokinetic studies in animal species. In addition, these assay methods allowed the full resolution between cabazitaxel and two pharmacologically active metabolites docetaxel and RPR123142 that were monitored/documented in some studies. Limits of quantification in plasma (LC-MS/MS methods) were in the range of 2.39-4.78 ng/mL for cabazitaxel, in the range of 2.50 to 5.00 ng/mL for docetaxel and 1.00 ng/mL for RPR123142. In most cases, bioanalytical methods allowed determination of plasma levels of cabazitaxel up to 4 to 168 hours post dosing, sufficient for an accurate determination of the pharmacokinetic parameters. Incurred sample short-term stability was demonstrated in rats and dogs for cabazitaxel.

Absorption

Exposure to cabazitaxel increased with dose after single or repeated IV administration in all species. The increase in exposure was approximately dose proportional in mice and more than dose proportional in rats and dogs.
No plasma accumulation was observed in mice, rats or dogs after five-daily or weekly administrations or after administration every 3 weeks.
No gender effect was observed in rats and dogs. Very low to low levels of metabolites RPR123142 (10-O-demethyl-cabazitaxel) and docetaxel (di-O-demethyl-cabazitaxel) were measured. The metabolic ratio of docetaxel versus cabazitaxel was 3.6% in tumour bearing mice after single administration while docetaxel was detected at only one sampling time at the highest dose tested (10 mg/kg) in the single toxicity study in rats. In addition, docetaxel was not detected in rabbits in the dose range finding toxicity study or in dogs in the single dose, 5-day and single-cycle toxicity studies. In the multiple cycle studies, the metabolic ratio of RPR123142 versus cabazitaxel ranged from 1% to 10% in rats while RPR123142 was only quantifiable at one sampling time in dogs, at the highest dose tested (0.5 mg/kg/administration).

Distribution

Cabazitaxel exhibited a large volume of distribution in all the species, suggestive of a large diffusion of the drug (in the gastrointestinal tract, kidneys, liver, in hematopoietic organs and in various glandular structures (pancreas, pituitary, submaxillary gland, ovaries, prostate and adrenals)).

Plasma protein binding of cabazitaxel was very high in mice (99.3%) and high in rats (95.5%), rabbits (91.4%), dogs (97.1%) and humans (91.9%) with no trend of saturation in the concentration range of 50 to 1000 ng/mL. At higher concentrations (up to 50 000 ng/mL) a trend toward saturation was observed in rabbits (above 1000 ng/mL), in mice (above 5000 ng/mL) and in dogs (above 10 000 ng/mL) and not in rats and humans.
Radioactivity exposure in the brain correlated with blood exposure and was therefore higher in mice than in rats and dogs. Low placental transfer (0.014%) of radioactivity (66% being Cazabitaxel) was observed in rat foetuses.

Metabolism

Cabazitaxel metabolism was investigated *in vitro* and/or *in vivo*, in the different animal species used in toxicological studies (Crl:CD-1(ICR)BR and C3H/HeN mouse, Sprague Dawley rat, New Zealand White rabbit, Beagle dog and Cynomolgus monkey) and in human.
The goal of the *in vivo* metabolic studies was to investigate the fate of the drug in animal species following a single IV administration. In addition, *in vitro* and *in vivo* metabolic studies allowed comparison of both Cabazitaxel metabolic rates and profiles between various animal species and human.

Cabazitaxel was extensively metabolised by the liver.
The main routes of biotransformation consisted of:

- 10-O-demethylation leading to RPR123142,
- 7-O-demethylation leading to RPR112698,
- hydroxylation on t-butyl moiety in the lateral chain, followed by cyclisation of the lateral chain giving rise to oxazolidine-type compounds,
- cleavage of Cabazitaxel leading to the loss of the taxane ring.

In vivo, the parent drug was the main circulating compound in mouse, rat and dog plasma (≥ 65% of the total radioactivity). Metabolism was the main elimination pathway of Cabazitaxel since almost no parent Cabazitaxel was excreted in urine or feces (<2%). No significant qualitative inter-species differences were noted in the metabolic profiles. All metabolites observed in human microsomes were also found in at least one animal species. At least seven metabolites were detected in human plasma but none of them (including the active metabolites RPR123142, RPR112698 and docetaxel) accounted individually for more than 10% on average of systemic exposure of parent drug. With metabolism data, the monkey and the dog (followed by the rabbit, mouse and by the rat) appeared the nearest species to human.

Excretion

Following a single IV administration of Cabazitaxel, the plasma clearance was high in rats (4.8 L/h/kg) and dogs (2.5 to 5.3 L/h/kg) and moderate in normal mice (0.9 to 1.1 L/h/kg) and in tumour bearing mice (1.7 L/h/kg).
The terminal half-life was medium in dogs (3.0 to 4.3 h), long in normal mice (5.1 to 7.6 h) and in rats (10 h), and even longer in tumour bearing mice (26 h). However, in tumour bearing mice a higher dose was given, allowing quantifiable levels at latter sampling times.

Following IV dosing in mice and rats, radioactivity was mainly excreted in the faeces via the bile (≥ 87% of the dose) and urinary excretion was minimal (≤ 4 %).

Following intravenous dosing [^{14}C]-cabazitaxel to lactating rats, a small amount of radioactivity was excreted into milk (between 0.23% and 1.5% of the dose).

Pharmacokinetic drug interactions

Cabazitaxel increased CYP3A enzyme activities *in vitro*, in rat hepatocytes. *In vitro* studies assessing the effect of potent CYP3A4 inhibitors and inducers on Cabazitaxel plasmatic exposure have not been performed. *In vitro* experiments using Human hepatocytes has shown that cabazitaxel is mainly metabolised by CYP3A (80-90%). Interaction prediction with static or dynamic modeling was not performed. However, two ongoing clinical studies, assessing the effect of ketoconazole (as a potent CYP3A4 inhibitor) and rifampicin (as a potent CYP3A4 inducer) will provide insight into the magnitude of this interaction in the clinical setting.

The *in vitro* study performed with a single cell model on transporters MRP1, MRP2 and BCRP, showed that Cabazitaxel is neither a substrate nor an inhibitor of such transporters.
However, since the model used has some limitations further investigations will be conducted to clarify this issue (see section 2.7).

2.3.4. Toxicology

Toxicology studies performed with cabazitaxel consisted of single-dose and 5-day studies in mice, rats and dogs, single-cycle studies (weekly administration) in mice and dogs, 4-week study (daily administration) in rats, 5-cycle study (1 administration every 3 weeks) in mice, 10-cycle study (1 administration every 3 weeks) in rats and 13-cycle study (1 administration every 3 weeks) in dogs.

During development of cabazitaxel, different schedules of administration were tested in preclinical toxicology studies, such as 5-day administration, weekly administration and once every 3 weeks administration to support the different schedules of administration that were envisaged (but were not necessarily tested) in the clinic. As the once every 3 weeks schedule of administration was retained for registration, the multiple-cycle toxicity studies in rats and dogs were conducted using this administration schedule.

Moreover, as treatment with microtubule stabilising drugs is often associated with neurotoxicity, several specific studies have been conducted in mice, which is the most sensitive species to assess neurotoxicity induced by cabazitaxel.

Pivotal studies were conducted using fully characterised batches of drug substance that are representative of the clinical and/or commercial product in terms of impurity content, including genotoxic impurities.

With the exception of the local tolerance in rabbits, all *in vivo* studies used the IV route. The duration of the infusions was approximately in the range of one minute to one-hour and was specified for each study. The chronic multiple-cycle toxicity studies in rats and dogs were conducted using the same duration of infusion as in clinical use (1-hour infusion).

Single dose toxicity

Single dose toxicity studies presented in table 1 were conducted in mice, rats and dogs (results not shown). Moreover, specific neurotoxicity studies have been conducted in mice following single dose administration.

Table 1: Single dose toxicity programme overview

Species (Strain)	**Method of Administration**	**Duration of Dosing**	**Doses (mg/kg)**	**Study number**
Single dose				
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	25, 50, 75 or 100 (75, 150, 225 and 300 mg/m^2)	RPR/RD/DS/CRVA 97-114
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	20, 30, 40 or 60 (60, 90, 120 and 180 mg/m^2)	RPR/RD/DS/CRVA 98-027
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	20, 30, 40 or 60 (60, 90, 120 and 180 mg/m^2)	RPR/RD/DS/CRVA 98-157
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	15, 30 or 45 (45, 90 and 135 mg/m^2)	RPR/RD/DS/CRVA 98-030
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	15, 30 or 45 (45, 90 and 135 mg/m^2)	RPR/RD/DS/CRVA 98-158
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	15, 20, 25, 30 or 40 (45, 60, 75, 90 and 120 mg/m^2)	RPR/RD/DS/CRVA 99-029

Mouse (CD_2F_1/CrlBR)	IV (1-minute or 1-hour infusion)	Single administration	10, 15, 20, 30 or 40 (30, 45, 60, 90 and 120 mg/m^2)	RPR/RD/SA/CRVA 99-115
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Single administration	40 (120 mg/m^2)	RPR/RD/SA/CRVA 99-173
Mouse (Crl:CD-1(ICR)BR)	IV (1-minute infusion)	Single administration	15 or 30 (45 and 90 mg/m^2)	RPR/RD/SA/CRVA 99-223
Rat Sprague-Dawley (Crl:CD-(SD)BR)	IV (1-minute infusion)	Single administration	2.5, 5 or 10 (15, 30 and 60 mg/m^2)	RPR/RD/DS/CRVA 98-028
Dog Beagle	IV (20-minute infusion)	Single administration	0.5, 1.5 or 2.5 (10, 30 and 50 mg/m^2)	RPR/RD/DS/CRVA 97-115
Dog Beagle	IV (1-hour infusion)	Single administration	0.25, 0.5 or 1 (5, 10 and 20 mg/m^2)	RPR/RD/DS/CRVA 98-029

Abbreviations: IV: intravenous

Toxicokinetic parameters:
The following tables (2 and 3) summarise toxicokinetics data obtained in single dose toxicity studies where toxicokinetics were performed.

Table 2: Toxicokinetic parameters in single-dose toxicity study in rats

		Cabazitaxel (Day 1)			**Docetaxel (Day 1)**	
Dose (mg/kg)	**Sex**	**Cmax (ng/mL)**	**tmax(min)**	**AUC(0–6h) (h.ng/mL)**	**Cmax (ng/mL)**	**tmax (min)**
2.5	M	579	2	218	BLQ	NA
	F	717	2	279	BLQ	NA
5	M	2275	2	860	BLQ	NA
	F	2073	2	1107	BLQ	NA
10	M	5238	2	3096	10.99	NA
	F	6483	2	4233	BLQ	NA

Table 3: Toxicokinetic parameters in single-dose toxicity study in dogs

Dose (mg/kg)	**Sex**	**Cabazitaxel (Day 1)**	
		Cmax (ng/mL)	**AUC(0–6h) (h.ng/mL)**
0.25	M	17.5	24.2
	F	26.5	25.0
0.5	M	64.8	79.1
	F	97.0	87.9
1	M	164	205
	F	360	391

Abbreviations: M: male; F: female
AUC (area under the curve) values were calculated by the trapezoidal rule from the beginning of injection to 6 hours after the end of injection
BLQ: plasma concentration below the limit of quantitation (2.39 ng/mL for cabazitaxel and 2.50 ng/mL for docetaxel)
Cmax: maximum plasma concentration observed; tmax: first time to reach Cmax

Neurotoxicity studies

Treatment with microtubule-stabilizing drugs is often associated with neurotoxicity (observed with paclitaxel and docetaxel) a potentially severe side effect limiting the clinical use of these agents. Consequently, several studies (determination of NOEL, evolution of lesions over time, modification of duration of infusion time) were performed in mice, the most sensitive species, to evaluate peripheral and central neurotoxicity induced by cabazitaxel. Specific pharmacokinetic and brain distribution studies were conducted in mice, rats and dogs to better understand the central neurotoxicity observed only in mice.

Four single-dose neurotoxicity (peripheral and central) studies were conducted in mice with cabazitaxel using different durations of infusion (1-minute or 1-hour) with different necropsy time points following the administration (See Table 4).

Table 4: Neurotoxicity studies in mice

Study Number	**Dose levels (mg/kg)**	**Duration of infusion**	**Observation period**	**No-Observable Effect Level for neurotoxicity (mg/kg)**
RPR/RD/DS/CRVA 98-030	15, 30 and 45 (45, 90 and 135 mg/m^2)	1-minute	2-week or 10-week	Central and peripheral: 15 (45 mg/m^2)
RPR/RD/DS/CRVA 98-158	15, 30 and 45 (45, 90 and 135 mg/m^2)	1-minute	2-week or 20-week	Central: 15 (45 mg/m^2) Peripheral: below 15 (below 45 mg/m^2)
RPR/RD/DS/CRVA 99-029	15, 20, 25, 30 and 40 (45, 60, 75, 90 and 120 mg/m^2)	1-minute	Days 5, 10, 15 and 28	Central: below 15 (below 45 mg/m^2) Peripheral: 15 (45 mg/m^2)

Study Number	Dose levels (mg/kg)	Duration of infusion	Observation period	No-Observable Effect Level for neurotoxicity (mg/kg)
RPR/RD/DS/CRVA 99-115	10, 15, 20, 30 and 40 (30, 45, 60, 90 and 120 mg/m^2)	1-minute or 1-hour	Days 5 and 15	Central: 10 (30 mg/m^2) Peripheral: 15 (45 mg/m^2)

Overall, in these studies, peripheral neurotoxicity was characterised by a non-extension of hindlimbs (when animals were suspended by the tail) and histopathologically by degeneration (numerous ellipsoids) of the sciatic nerves and lumbosacral nerve roots. These histopathological changes were not reversible after 10 or 20 weeks following a single administration. Considering all the above referenced neurotoxicity studies, the lowest NOEL in mice for peripheral neurotoxicity was 15 mg/kg (45 mg/m^2) after single intravenous administration over 1 hour and was considered to be 10 mg/kg (30 mg/m^2) after single intravenous administration over 1 minute.

In addition, central neurotoxicity was characterised histopathologically by neuron necrosis and/or vacuolation in the brain and axonal swelling and degeneration in the cervical spinal cord. Brain findings were not present following a 20-week observation period.

Considering all the above referenced neurotoxicity studies, the lowest NOEL in mice for central neurotoxicity was 10 mg/kg (30 mg/m^2) after a single intravenous administration over 1 minute or 1 hour. With a NOEL equal to 10 mg/kg (30 mg/m^2) [$AUC_{0\text{-}168}$: 10800 ng.h/mL], safety margin for neurotoxicity finding was equal to 7.

Repeat dose toxicity

Pivotal repeat dose toxicity studies have been performed in rats and dogs using the scheme of administration used in clinical practice (administration once every 3 weeks per cycle) up to 10 and 13-cycles respectively (see table 5 for a repeat dose toxicity programme overview).

Table 5: Repeat dose toxicity programme overview

Species (Strain)	Method of Administration	Duration of Dosing	Doses (mg/kg/administration)	Study number
Repeat-dose				
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	5 days	5, 7.5, 10 or 12.5 (15, 22.5, 30 and 37.5 mg/m^2)	RPR/RD/DS/CRVA 97-116
Dog Beagle	IV (20-minute infusion)	5 days	0.1, 0.2 or 0.3 (2, 4 and 6 mg/m^2)	RPR/RD/DS/CRVA 97-117
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	5 days	1, 3, 5 or 7 (3, 9, 15 and 21 mg/m^2)	RPR/RD/DS/CRVA 98-031

Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	5 days	1, 3 or 5 (3, 9 and 15 mg/m^2)	RPR/RD/DS/CRVA 98-231
Mouse (CD_2F_1/CrlBR)	IV (1-minute infusion)	Weekly: Once daily on Days 1, 8, 15 and 22	5, 15, 30 or 40 (15, 45, 90 and 120 mg/m^2)	RPR/RD/DS/CRVA 98-366
Mouse (CD_2F_1/CrlBR)	IV (1-hour infusion)	5-cycle: Once daily on Days 1, 22, 43, 64 and 85	5, 10, 15 or 30 (15, 30, 45 and 90 mg/m^2)	RPR/RD/SA/CRVA 99-146
Rat Sprague-Dawley (Crl:CD-(SD)BR)	IV (1-minute infusion)	5 days	0.25, 0.5 or 1 (1.5, 3 and 6 mg/m^2)	RPR/RD/DS/CRVA 98-032
Rat Sprague-Dawley (Crl:CD-(SD)BR)	IV (1-minute infusion)	4 weeks	0.05, 0.10 or 0.30 (0.3, 0.6 and 1.8 mg/m^2)	SA 99-260
Rat Sprague-Dawley (Crl:CD-(SD)BR)	IV (1-hour infusion)	10-cycle: Single dose every 3 weeks	1, 5 or 20/10 (6, 30 and 120/60 mg/m^2)	TSK0038
Dog Beagle	IV (1-hour infusion)	5 days	0.025, 0.05 or 0.1 (0.5, 1 and 2 mg/m^2)	RPR/RD/DS/CRVA 98-033
Dog Beagle	IV (1-hour infusion)	Weekly: Once daily on Days 1, 8, 15 and 22	0.125, 0.225 or 0.450/0.325 (2.5, 4.5 and 9/6.5 mg/m^2)	RPR/RD/SA/CRVA 99-026
Dog Beagle	IV (1-hour infusion)	13-cycle: Single dose every 3 weeks	0.1, 0.25 or 0.5 (2, 5 and 10 mg/m^2)	TSK0037

Abbreviations: IV: intravenous

The results of the two pivotal studies (10-cycle rat and 13-cycle dog) are presented in Table 6 below. The two No observable adverse effect level (NOAEL) for these pivotal studies are below 1 mg/kg/adm and equal to 0.1 mg/kg/adm respectively; the two Highest non severely toxic dose (HNSTD) are equal to 1 and 0.5 respectively. For the lens findings in the rat study observed at 20/10 mg/kg/adm, the NOAEL is 5 mg/kg/adm.

Table 6: Summary of Repeat-dose toxicity pivotal studies

Study ID GLP Status	Species/Sex/ Number/Group	Dose/Route	Duration	NOAEL (mg/kg /day)	Major findings
TSK0038 GLP	Rat Sprague-Dawley (Crl:CD-(SD)BR) (15/sex/group)	1, 5 and 20/10 IV (1-hour infusion) (6, 30 and 120/60 mg/m2)	10-cycle: Single dose every 3 weeks	NOAEL < 1 HNSTD = 1	The dose of 20 mg/kg was not tolerated was reduced to 10 mg/kg/adm. The main histopathological changes leading to mortality and early termination of treatment consisted of pronounced depletion of the lymphohematopoietic system (thymus, lymph nodes, spleen, bone marrow). Death of one female at 5 mg/kg/adm and produced a few clinical signs (hairloss, loss of whiskers, tooth abnormalities) at 5 mg/kg/adm in both sexes. Microscopic findings at 5: decreased lymphocytes in lymphoid tissues (thymus, spleen, lymph nodes and Peyer's patches) and decreased hematopoietic cells in the bone marrow (with secondary infection); seminiferous tubule atrophy in the testes; nerve fiber degeneration in the sciatic nerve; atrophic and dysplastic changes in the incisor teeth; At 1 mg/kg/adm: microscopic findings were limited to the gastrointestinal tract, lymphoid tissues, bone marrow, sciatic nerve, ovary, seminal vesicle and spleen (increased pigment deposit), and were generally similar to but less severe than those observed at the higher doses. At 20/10 mg/kg/adm: corneal single cell necrosis and lens fiber swelling/degeneration in the eyes, epithelial atrophy and degeneration/regeneration in the prostate, Kupffer's cell pigmentation and bile duct degeneration/regeneration in the liver.
TSK0037 GLP	Dog Beagle (3/sex/group)	0.1, 0.25 and 0.5 IV (1-hour infusion) (2, 5 and 10 mg/m^2)	13-cycle: Single dose every 3 weeks	NOAEL = 0.1 HNSTD = 0.5	No unscheduled deaths. Macroscopic observations of red foci/areas were noted in the stomach and/or colon from some males and females at 0.5 mg/kg/adm, and were considered likely secondary to the Cabazitaxel related microscopic mucosal changes. At the end of the 3-day observation period, compound-related microscopic observations attributable to the cytotoxic activity of Cabazitaxel were present in the gastrointestinal tract at 0.25 and 0.5 mg/kg/adm and in the gut-associated lymphoid tissue (GALT), bone marrow (sternum) and epididymis at 0.5 mg/kg/adm. Microscopic findings in the gastrointestinal tract consisted of a minimal increase in mucosal epithelial single cell necrosis in the esophagus, stomach and/or duodenum at 0.5 mg/kg/adm, and minimal to mild mucosal epithelial regenerative hyperplasia in the small and large intestines of all dogs at 0.5 mg/kg/adm and in one female at 0.25 mg/kg/adm.

Toxicokinetic parameters:
The following table summarises toxicokinetics data obtained in repeat dose toxicity studies where toxicokinetics were performed.

Table 7: Toxicokinetic parameters in Rat 5-days and 10-cycle, Dog 5-days and 13-cycle studies

Study	Species	Time	Dose	Cmax (ng/mL)		AUC (h.ng/mL)	
				Cmax		AUC 0-6h	
				Male	Female	Male	Female
5-day toxicity study in rats RPR/RD/DS/CRVA98-032	Rat	Day 1	0.25 0.5 1	25.1 38.7 140	25.1 42.6 16	11.8 28.2 78.2	9.1 15.6 63.4
		Day 5	0.25 0.5 1	30.4 44.2 149	22.4 35.0 185	15.4 24.2 79.4	8.3 14.4 86.5
				Cmax		AUC 0-24h	
10-cycle toxicity study in rats (Pivotal study) TSK0038	Rat	Cycle 1 (Day 0)	1 5 20/10	61.3 771 5650	16.3 476 4950	165 1160 10 500	91.7 772 8390
		Cycle 5 (Day 84)	1 5 20/10	46.5 771 1040	35.8 516 1320	199 1180 1950	138 749 1880
		Cycle 10 (Day 189)	1 5 20/10	65.8 665 NA	47.2 531 1400	240 1030 NA	129 760 1900
				Cmax		AUC 0-2h	
5-day toxicity study in dogs RPR/RD/DS/CRVA98-033	Dog	Day 1	0.025 0.05 0.1	BLQ BLQ 4.60±0.964	BLQ BLQ 5.95±1.04	NA NA 5.46±1.10	NA NA 6.15±0.524
		Day 5	0.025 0.05 0.1	BLQ BLQ 5.45±0.826	BLQ 2.93±0.401 5.92±0.895	NA NA 7.36±2.27	NA NA 7.83±3.08
				Cmax		AUC 0-24h	
13-cycle toxicity study in dogs (Pivotal study) TSK0037	Dog	Cycle 1 (Day 1)	0.10 0.25 0.50	7.36 64.8 139	9.38 52.5 174	NC 63.4 156	10.1 72.7 198
		Cycle 6 (Day 106)	0.10 0.25 0.50	7.21 37.0 63.7	7.09 24.5 134	8.73 36.2 87.2	8.09 28.2 186
		Cycle 13 (Day 253)	0.10 0.25 0.50	7.78 29.8 72.5	8.38 38.8 144	9.65 39.7 114	8.18 50.8 203

Genotoxicity

Table 8 : Genotoxicity studies

Species (Strain)	Method of Administration	Duration of Dosing	Doses (mg/kg)	Study number
Genotoxicity in vitro				
Bacterial reverse mutation test – Ames Test (Salmonella typhimurium TA1535, TA1537, TA98, TA100 and TA102	Plate incorporation medium (with and without S9 mix) and preincubation method (with S9 mix)	48 hours	10, 50, 100, 500 and 1000 µg/plate with plate incorporation treatment method; 50, 100, 500, 1000 and 2500 µg/plate with preincubation treatment method	RPR/RD/DS/CRVA 98-020

Bacterial reverse mutation test – Ames Test (Salmonella typhimurium TA1535, TA1537, TA98, TA100 and TA102	Plate incorporation medium (with and without S9 mix) and preincubation method (with S9 mix)	48 hours	10, 50, 100, 500 and 1000 µg/plate with and without S9 mix	RPR/RD/DS/CRVA 98-156
Chromosome aberration test in human peripheral blood lymphocytes	In cell culture	3 or 20 hours	- first assay: 0.0001 to 0.1 µg/ml with and without S9 mix - second assay: 0.00001 to 0.01 µg/ml without S9 mix and 0.001 to 0.1 µg/ml with S9 mix	RPR/RD/DS/CRVA 98-022
Genotoxicity *in vivo*				
Bone marrow micronucleus test – rats, Sprague-Dawley (Crl:CD-(SD)BR)	IV (1-minute infusion)	Single administration	0.5, 1 or 1.5 (3, 6 or 9 mg/m^2)	RPR/RD/DS/CRVA 98-023

Abbreviations: IV: intravenous

Cabazitaxel was found to be negative in the bacterial reverse mutation test (Ames test). The effects observed in the in-vitro chromosome aberration test (increased number of polyploid cells) and the increased incidence of micronucleated polychromatic erythrocytes noted in the rat bone marrow micronucleus test were consistent with the pharmacological activity of the compound (inhibition of tubulin depolymerization).

Carcinogenicity

According to the ICH Topic S9, carcinogenicity study is not required to support marketing for therapeutics intended to treat patients with advanced cancer, but cabazitaxel can be considered as a carcinogenic agent due to the genotoxic properties.

Reproduction Toxicity

The following table summarises the reproductive and developmental studies performed with cabazitaxel

Table 9: Summary of reproductive and developmental studies

Study type/ Study reference / GLP Status	**Species; Number/ sex/group**	**Dose (mg/kg /day) Route**	**Dosing period**	**NOAEL (mg/kg/day)**	**Major findings**
FERTILITY AND EARLY EMBRYONIC DEVELOPMENT					
Male fertility study RPR/RD/SA /CRVA 99-264 GLP	Rat Sprague-Dawley (Crl:CD-(SD)BR) (26/sex/group)	0,05 0,10 or 0,30/ 0,20 IV (1-minute infusion)	Sprague-Dawley rats (9 weeks of age) were treated with Cabazitaxel by intravenous injection once daily for 70 days prior to cohabitation, during cohabitation with untreated females maximum 10 days) and after cohabitation through Week 12.	NOAEL (paternal toxicity) = 0.1 mg/kg/d NOAEL for mating performance and male fertility = 0.2 mg/kg/d	**0.3/0.2 mg/kg/day :** **-** 1 male rat was found dead on Day 18 - reduction in food consumption Mating performance, delay before mating and pregnancy rate were comparable in all groups.
Female fertility study RPR/RD/SA	Rat Sprague-Dawley (Crl:CD-(SD)BR) (26/sex/grou	0,05 0,10 0.20 IV (1-minute	Female Sprague–Dawley rats (10 weeks of age) were used to determine the effects of Cabazitaxel on mating performance, fertility and early embryonic development	Maternal NOAEL = 0.1 mg/kg/day NOAEL on female	- No deaths - No compound-related effects on mating performance and fertility. **0.2 mg/kg/day :** decrease in mean body

Study type/ Study reference / GLP Status	Species; Number/ sex/group	Dose (mg/kg /day) Route	Dosing period	NOAEL (mg/kg/day)	Major findings
/CRVA 00-069 GLP	p)	infusion)	when administered by intravenous injection once daily for 15 days prior to cohabitation, during cohabitation with untreated males (maximum 12 days) and through gestational Day 6.	fertility = 0.2 mg/kg/day Developmental NOAEL = 0.05 mg/kg/day	weight gain, associated with decrease in food intake. decrease in corporea lutea and implant sites, and increase in preimplantation loss. decrease in the number of total live fetuses. **0.1 mg/kg/day :** increase in postimplantation loss (early resorptions).
EMBRYO-FETAL DEVELOPMENT					
RPR/RD/DS /CRVA 99-018 GLP	Rat Sprague-Dawley (Crl:CD-(SD)BR) (29F/group)	0,04 0,08 0,16 IV (1-minute infusion)	Mated female Sprague-Dawley rats (10 weeks of age) received Cabazitaxel in vehicle at 0.04, 0.08 or 0.16 mg/kg/day by intravenous injection (tail vein) once daily for 12 days from Gestational Days 6 through 17.	Maternal NOAEL = 0.08 mg/kg/day Developmental NOAEL = 0.04 mg/kg/day	**0.16 mg/kg/day :** increase in postimplantation loss, decrease in mean fetal weight associated with delay in skeletal ossification, increase in incidence of skeletal variations (misaligned sternebra and supernumerary rib) **0.08 mg/kg/day :** decrease in mean fetal weight associated with slight delay in skeletal ossification, increase in incidence of skeletal variations (misaligned sternebra and supernumerary rib).
RPR/RD/CR VA/SM 98-035 GLP	Rabbit (NZW) (8F/group)	0.02, 0.04 or 0.08 IV (3-minutes infusion)	Mated female New Zealand white rabbits (19-22 weeks of age) received Cabazitaxel in vehicle at 0.02, 0.04 or 0.08 mg/kg/day by intravenous injection (ear vein) once daily for 13 days from gestational Days 6 through 18.	Maternal NOAEL = 0.02 mg/kg/day	**0.08 mg/kg/day:** decrease in total white blood cells (maximum -56%, primarily due to a decrease of -97% in neutrophils) and in red blood cell parameters (maximum -14% for hematocrit). **0.04 and 0.08 mg/kg/day:** Decrease in food consumption and decrease in body weight gain, and reduced feces. decrease in absolute and percent reticulocytes (maximum -65%) and in platelets (maximum -44%)
Study RPR/RD/DS /CRVA	Rabbit (NZW) (22F/group)	0.01, 0.02 or 0.03 IV (3-	Mated female New Zealand white rabbits (16-20 weeks of age) received Cabazitaxel in vehicle at 0.01, 0.02 or 0.03	Maternal and the developmental NOAELs were above 0.03	No compound–related deaths, clinical signs or effects on body weight and food consumption at any dose level during the

Study type/ Study reference / GLP Status	Species; Number/ sex/group	Dose (mg/kg /day) Route	Dosing period	NOAEL (mg/kg/day)	Major findings
99-019 GLP		minutes infusion)	mg/kg/day by intravenous injection (ear vein) once daily for 13 days from gestational Days 6 through 18.	mg/kg/day	study. No signs of irritation were noted at the injection sites. The pregnancy rate was satisfactory in all groups. There were no compound–related effects on litter data, on embryo-fetal survival, on fetal weight or on the type or incidence of external, visceral or skeletal fetal observations.

Cabazitaxel did not affect mating performances or fertility of male and female rats.
Cabazitaxel induced embryo-foetal toxicity in rats, linked with maternal toxicity and consisting of foetal deaths and decreased mean foetal weight associated with delay in skeletal ossification. No foetal abnormalities were observed in rats and rabbits. However, regarding the study performed in the rabbit, the choice of the high dose (0.03 mg/kg/day) was questionable given the lack of maternal toxicity at this dose level.

Local Tolerance

Following intravenous or intra-arterial administration, cabazitaxel solutions at concentrations of 1.0 or 2.0 mg/mL in PS80 and ethanol diluted in 5% glucose were not irritating in the ears of male New Zealand White rabbits. However, following paravenous administration, cabazitaxel solutions showed microscopic evidence of dermal irritation that was likely related to the vehicle with possible exacerbation by cabazitaxel. These concentrations are higher than those expected in human therapeutic conditions (clinical concentrations range: 0.10 to 0.30 mg/mL).

Other toxicity studies

Mechanistic studies were performed by the Applicant to explore the pathogenesis of diarrhoea observed in dogs investigated. The results showed that cabazitaxel-induced diarrhea was primarily related to a loss of mucosal barrier integrity.

In order to qualify impurities, specific studies were performed with batches spiked with different impurities tested in multiple cycle toxicity in rats and dogs and in the Ames test.

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant has performed an ERA. According to the data provided, cabazitaxel will not result in a significant environmental impact.

2.3.6. Discussion on non-clinical aspects

Tubulin, the protein component of microtubules, is the main target of taxanes, such as docetaxel and paclitaxel. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilisation of microtubules, which results in the inhibition of mitotic and interphase cellular functions.
Cabazitaxel was as potent as docetaxel in stabilising microtubules.

The Applicant has provided numerous *in vitro* and *in vivo* studies investigating the antitumour activity of Cabazitaxel in several tumour cell lines and various cancer models sensitive or resistant to docetaxel.

Safety pharmacology studies did not indicate that Cabazitaxel had adverse effects on the central nervous, respiratory, cardiovascular and gastro-intestinal systems after intravenous administration.

Pharmacokinetics studies were performed in mice, rats and dogs.
Cabazitaxel increased CYP3A enzyme activities *in vitro*, in rat hepatocytes. *In vitro* studies assessing the effect of potent CYP3A4 inhibitors and inducers on Cabazitaxel plasmatic exposure have not been performed. *In vitro* experiments using Human hepatocytes has shown that cabazitaxel is mainly metabolised by CYP3A (80-90%). Interaction prediction with static or dynamic modeling was not performed. However, two ongoing clinical studies, assessing the effect of ketoconazole (as a potent CYP3A4 inhibitor) and rifampicin (as a potent CYP3A4 inducer) will provide insight into the magnitude of this interaction in the clinical setting.

Pharmacokinetic drug interaction studies are not sufficient to fully characterise the PK profile of Cabazitaxel. A further *in vitro* study, using another cell model, will be conducted to clarify whether Cabazitaxel is or not a MRP1, MRP2 inhibitor and a BCRP substrate/ inhibitor.

The results of the general toxicity studies show that the principal adverse effects of cabazitaxel are consistent with the pharmacological (antimitotic) activity of a taxane-type antineoplastic compound and resemble those reported for other taxane anticancer drugs.

Cabazitaxel predominantly affected tissues with a high cell turnover in rats and dogs such as the bone marrow (cellular depletion), the liver (hepatocellular necrosis), the haematopoietic and lymphoid systems (atrophy and/or increased lymphocytolysis), the gastrointestinal tract (epithelial cell necrosis and/or cell degeneration/regeneration) and the male reproductive system. Most of these effects were reversible and therefore considered compatible with an administration every 3 weeks. These findings are well correlated with the distribution of the radioactivity in rats where high concentrations were observed in bone marrow, haematopoietic and lymphoid systems and the gastrointestinal tract.

There were some similarities in the toxicological profile of cabazitaxel between preclinical and clinical studies, as major expected effects observed in clinic are haematological findings (mainly neutropenia and its complications) and gastrointestinal disorders (mainly diarrhoea, nausea and vomiting)

Due to higher sensitivity of dogs and rats to cabazitaxel compared to humans (as this is also the case for other marketed taxanes, docetaxel or paclitaxel), the limiting toxicity was obtained at much higher levels of exposure in humans compared to rats and dogs. Consequently, the calculation of exposure ratios showed that it is not possible to provide safety margins and these calculations do not provide a reliable indicator for the assessment of the risk in humans.

Increased hepatic serum chemistry parameters, arteriolar/periarterolar necrosis in the liver, bile ductule hyperplasia and/or hepatocellular necrosis were observed in dogs after single-dose, 5-day and single-cycle (weekly) administration and in rats after 10-cycle administration. These findings are included in section 5.3 of the summary of product characteristics (SmPC). In clinical studies, transient increase of bilirubin and transaminases levels and liver injuries (hepatitis or cholestasis for example) were occasionally observed.

Peripheral neurotoxicity was observed in mice with single, 5-day, weekly and 5-cycle (1 infusion every 3 weeks) administrations and in rats with single and 10-cycle administrations. Sensory neuropathy was observed in clinic with cabazitaxel and it was already observed with other marketed taxanes (docetaxel, paclitaxel).

Central neurotoxicity was noted in mice after a single administration, after a 5-cycle administration (1 infusion every 3 weeks) with a NOEL of 10 mg/kg (30 mg/m2) or after a single-cycle administration (weekly) with a NOEL of 5 mg/kg (15 mg/m²)).
Occurrence of central neurotoxicity in mice correlate well with the higher blood exposure achieved in this species compared to rats or dogs. In addition, brain exposures in mice were markedly increased after 5 repeated administrations once every 3 weeks. However, the brain exposure at the NOEL after the 5th administration (19 627 ng.h/g) remained below the lower brain exposure value for which the central neurotocixity was observed after single administration in mice (45 400 ng Eq.h/g). The central neurotoxicity was observed only in mice and not in the other species including humans.

Adverse reactions not observed in clinical studies, but seen in rats during repeat-dose toxicity studies at exposure levels higher than clinical exposure levels and with possible relevance to clinical use were

eye disorders characterised by subcapsular lens fiber swelling/degeneration. These effects were partially reversible after 8 weeks.

The exposure achieved in man at the recommended therapeutic dose is equivalent to exposure in rats at the NOEL for microscopic findings in the lens in the 10-cycle (1 administration every three weeks) IV toxicity study in rats and at least 2-fold lower than exposure at the high dose level that resulted in microscopic ocular findings and lethality in rats. This effect was not observed in mice and dogs nor in other rat toxicity studies. No effect on lens was reported in patients. The applicant states that in clinical studies, one patient was reported to have cataracts, however the effect of age and concurrent use of prednisone for the treatment of prostate cancer in initiating or aggravating the cataract cannot be excluded. These findings are included in the SmPC.
Cabazitaxel did not induce mutations in the bacterial reverse mutation (Ames) test. Cabazitaxel increased numerical aberration with and without metabolic activation in the *in vitro* chromosome aberration test and was positive in the micronucleus test. These results are consistent with its pharmacological activity (inhibition of tubulin depolymerisation).

Cabazitaxel induced embryofetal toxicity in rats treated intravenously once daily from gestational days 6 through 17, linked with maternal toxicity, and consisted of foetal deaths and decreased mean foetal weight associated with delay in skeletal ossification. Cabazitaxel did not produce fetal abnormalities in rats and rabbits and did not affect mating performances or fertility of male and female rats. However, in repeated-dose toxicity studies, degeneration of seminal vesicle and seminiferous tubule atrophy in the testis were observed in rats, and testicular degeneration (minimal epithelial single cell necrosis in epididymis), was observed in dogs.
In rats, cabazitaxel and its metabolites are excreted in maternal milk at a quantity up to 1.5% of administered dose over 24 hours.
The placental transfer of drug-related material demonstrated in rats validates the observations recorded in the embryofetal toxicity studies. It should be noted that cabazitaxel is indicated in hormone refractory metastatic prostate cancer.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the results of the non-clinical safety studies suggest that the principal adverse effects of cabazitaxel are consistent with the pharmacological (anti-mitotic) activity of a taxoid –type antineoplastic compound and resemble those reported for other taxoid anticancer drugs. In view of its therapeutic indication of the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen, it is considered that there are no major objections or other concerns.
Regarding pharmacokinetic drug interactions, the Applicant is performing additional study to characterise the profile of the drug and possible interactions with other drugs (see 2.6).

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme for the proposed indication includes the following studies:

- Three phase I dose finding studies in patients with solid tumours (TED6188, TED6189 and TED6190)
- One phase II study in patients with taxane and/or anthracycline-resistant metastatic breast cancer (ARD6191)
- One phase III study designed to evaluate the efficacy and safety of Cabazitaxel versus mitoxantrone in HRPC patients previously treated with a docetaxel containing regimen (EFC6193).

The indication applied for initially and finally approved was the following:
Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.

GCP

In accordance with Community Directives, the Applicant has provided a statement regarding GCP compliance. The Applicant also states compliance with international & national laws/regulations and that Ethics Committee approval was sought prior to study initiation.

No non-compliance issues or specific GCP triggers have been revealed during the assessment of the dossier. A GCP inspection was not considered necessary for this Application.

- Tabular overview of clinical studies

Clinical studies with Cabazitaxel submitted in support of this Application are listed in the table below:

Table 10: Cabazitaxel clinical studies

Name	Description	N (patients recruited)
TED 6188	Dose-finding, safety, pharmacokinetics, efficacy	21
TED 6189	Dose-finding (IV) & oral bioavailability, safety, PK, efficacy	31/11*
TED 6190	Dose-finding (IV) & oral bioavailability, safety, PK, efficacy	25/11*
BEX 6702	PK (excretion balance), metabolism, safety	4
MEH 0033	Metabolic profiling in plasma, urine and faeces	4
EFC 6193	Efficacy, safety, PK.	67**
POH 0124	Population pharmacokinetics. Pooled data from TED 6188, TED 6189, TED 6190, ARD 6191, EFC 6193.	170***
POH 0258	Pharmacokinetic/pharmacodynamic analyses. Pooled data from TED 6188, TED 6190, ARD 6191, EFC 6193.	170***
TCD 6945	Dose-finding, efficacy, safety, PK.	34
ARD 6191	Efficacy, safety, PK	71
EFC 6193	Efficacy, safety, PK	755

*IV dose escalation/Oral bioavailability; **PK analysis; ***pooled data.

2.4.2. Pharmacokinetics

Absorption

Results taken from the phase I study TED 6188 indicated that Cabazitaxel exhibited a high clearance (CL) (mean CL, 44.7 L/h/m²) representing approximately 88% of the hepatic blood flow, a large distribution within the body (mean Vss, 2484 L/m²) and a long terminal half-life (mean, 62.0h). The PK was time independent up to 3 consecutive chemotherapy cycles. The PK analysis showed a dose proportional increase in $AUC_{(0\text{-}48h)}$ over the dose range tested. This finding indicated that the PK of XRP6258 following a 1-hour i.v. infusion is linear over 10-30 mg/m². The ex vivo plasma protein binding was high (91.6%) and comparable to the in vitro data. Similar results could be found in study **TED 6190**.

The descriptive statistics of the PK parameters taken from studies TED6188, TED6190, ARD6191 and from the pivotal phase 3 study EFC6193 are summarised in the following table and table 12

Table 11: Descriptive statistics of PK parameters (n=145) at cycle 1

	CBZ+PRED (N=67)	<25 mg/m² CBZ (N=57)	≥25 mg/m² CBZ (N=21)	Overall (N=145)
AUC (ng.h/ml) at cycle 1				
Mean	991	1018	982	1000
Min	530	262	491	262
5% percentile	656	364	508	491
50% percentile	907	911	879	906
95% percentile	1732	1722	1591	1728
Max	2494	1909	1822	2494
C_{max} (ng/ml) at cycle 1				

	CBZ+PRED (N=67)	<25 mg/m² CBZ (N=57)	≥25 mg/m² CBZ (N=21)	Overall (N=145)
Mean	226	220	325	238
Min	49.7	48.0	64.3	48.0
5% percentile	74.9	61.8	90.8	66.0
50% percentile	171	141	197	165
95% percentile	846	660	732	732
Max	1368	1380	1104	1380
CL (L/h) at cycle 1				
Mean	52.6	39.4	54.2	47.6
Min	20.1	15.5	15.4	15.4
5% percentile	26.0	18.4	22.3	20.1
50% percentile	51.3	33.8	58.1	48.5
95% percentile	76.5	75.5	85.5	76.9
Max	94.3	98.3	90.5	98.3
CLf at cycle 1				
Mean	0.99	1.49	1.11	1.21
Min	0.5	0.5	0.5	0.5
5% percentile	0.62	0.63	0.56	0.62
50% percentile	0.93	1.41	0.82	0.98
95% percentile	1.83	2.58	2.13	2.37
Max	2.4	3.1	3.1	3.1
Cumulative AUC (ng.h/ml)				
Mean		6155	6155	
Min		845	845	
5% percentile		1141	1141	
50% percentile		5927	5927	
95% percentile		11242	11242	
Max		14963	14963	

CBZ = Cabazitaxel, PRED = Prednisone/Prednisolone, CLf=mean CL/CL estimate

Table 12: Descriptive statistics of AUC and C_{max} by dose level (n=145) at cycle 1

	CBZ+ PRED (N=67)	10 mg/m² CBZ (N=6)	15 mg/m² CBZ (N=6)	20 mg/m² CBZ (N=45)	25 mg/m² CBZ (N=16)	30 mg/m² CBZ (N=5)	Overall (N=145)
AUC (ng.h/ml) at cycle 1							
Mean	991	419	815	1126	1026	842	1000
Min	530	262	525	389	491	690	262
5% percentile	656	261	525	477	492	690	491
50% percentile	907	403	734	1171	926	847	906
95% percentile	1732	591	1261	1722	1822	1048	1728
Max	2494	591	1261	1909	1822	1048	2494
C_{max} (ng/ml) at cycle 1							
Mean	226	112	174	240	325	325	238
Min	49.7	61.8	48.0	60.8	64.3	169	48.0
5% percentile	74.9	61.8	48.1	67.0	64.3	169	66.0
50% percentile	171	91.5	120	156	187	245	165
95% percentile	8456	187	459	660	1104	569	732
Max	1368	187	459	1380	1104	569	1380

CBZ = Cabazitaxel, PRED = Prednisone/Prednisolone

A population pharmacokinetic model was developed and validated with data from 170 patients treated with cabazitaxel included in five studies (TED6188, TED6189, TED6190, ARD6191 in breast cancer patients, and EFC6193 in mHRPC patients). The main objective of this analysis was to develop and qualify a PopPK model for cabazitaxel administered in several studies performed in patients with advanced solid tumours and to investigate the influence of key demographic parameters (e.g. body surface area, age, etc.), renal function (measured by creatinine clearance) and hepatic function (measured by bilirubin, ALT, AST, and ALK), disease status (tumour type) and concomitant medication (CYP inducers). Results indicated that Interindividual variability of cabazitaxel clearance was significantly related to body surface area and tumour type.

Distribution

The Cabazitaxel pharmacokinetic profile was consistent with a 3-compartment pharmacokinetic model and was characterised by rapid initial and intermediate phases with population half-lives of 4.4 minutes and 1.6 hours, respectively, and by a long terminal phase with a half-life of 95.1 hours. Cabazitaxel exhibited a large volume of distribution (population PK estimate of 4870 L, [2640 L/m² for a median body surface area [BSA] of 1.84 m²]).

Protein binding studies were performed on human plasma and on purified isolated plasma proteins (albumin, lipoprotein (high-density lipoprotein [HDL], low-density lipoprotein [LDL], very low-density lipoprotein [VLDL]) and α1-acid glycoprotein [AAG]).The mean ex-vivo human plasma protein binding of Cabazitaxel was 91.6%, in agreement with in vitro data. Cabazitaxel showed a high binding to human serum albumin (82.0%) and lipoproteins (87.9% for HDL, 69.8% for LDL, and 55.8% for VLDL) and a low binding to α1 glycoprotein acid (17.8%).

After a 1-hour IV administration of [^{14}C]-Cabazitaxel, the mean value of the radioactivity blood to plasma ratio at mid and end of infusion, where unchanged drug was the major component circulating in plasma (86%), was 1.1 (BEX6702 study).This value is in agreement with the in vitro values of the blood to plasma ratio for Cabazitaxel (mean: 0.90 and 0.99). This finding indicated that Cabazitaxel was equally distributed between plasma and blood cells and confirmed that plasma was an appropriate matrix for monitoring the pharmacokinetics of Cabazitaxel.

Metabolism

In vitro data

In vitro studies performed on human microsomal fractions indicated that Cabazitaxel was rapidly and extensively metabolised in numerous metabolites. The main metabolic pathways consisting of (1) O-demethylations leading to formation of RPR123142 (10-O-demethylated derivative), RPR112698 (7-O-demethylated derivative) and combined 7- and 10-O-demethylations (docetaxel), (2) hydroxylation on the tert-butyl group of the lateral chain, followed by a cyclization of the lateral chain. Combinations of these metabolic pathways were observed (hydroxylated derivative on the t-butyl moiety of docetaxel (RPR104952) and hydroxyoxazolidine derivatives of docetaxel (isomers RPR111026 and RPR111059). Similar biotransformation pathways, that only involved Phase 1 reactions, were observed *in vivo*.

In vivo data

Four metabolic pathways have been identified in human (study MEH 0033). These metabolites have previously been found to be main metabolites of docetaxel (however, docetaxel itself was only detected at very low levels in plasma and faeces).
First two O-demethylations on the taxane ring accounting together for 40% of the dose, one leading to RPR112698 (24% dose) and the other leading to RPR123142 (16% dose), then hydroxylation on t-butyl moiety on the lateral chain followed by cyclisation of the lateral chain giving rise to oxazolidine-type compounds (21% of the dose) and cleavage of the parent drug leading to the loss of the taxane moiety, a minor pathway only detected at low levels in plasma and urine.

Elimination

Excretion:

Results are mainly taken from studies BEX 6702. This study was a phase 1, open study investigating the disposition of 25 mg/m² [14C]-XRP6258 (50 µCi) administered as a 1-hour intravenous infusion to patients with advanced solid tumours (BEX6702). Four patients with advanced solid tumours received a single 1-hour IV infusion of [14C]-Cabazitaxel at 25 mg/m² (50 µCi). Radioactivity was largely excreted in the faeces (76.0% of the dose), whereas the urinary route contributed markedly less (3.7% of the dose) over 2 weeks. The mean recovery was 79.7% of the dose within 2 weeks with individual values ranging from 72.6% to 91.2% (with approximately 1% of the dose still being excreted in faeces at the final collection).

Study MEH 0033 also showed that following intravenous infusion of [14C]- XRP6258 at 25 mg/m² (4 patients with advanced solid tumours), radioactivity was mainly recovered in faeces (63 to 77% of the dose within 7 to 10 days) while a further 3 to 4% of the dose was excreted in urine within 4 to 5 days. No unchanged compound was detected in faeces and 1.6-3.0% of the dose was excreted as parent XRP6258 in urine, revealing an extensive metabolism of XRP6258 in human.

Dose proportionality and time dependencies

In the 1-hour IV infusion every-3-weeks schedule, no major deviation to the dose proportionality was observed from 10 to 30 mg/m² and from 10 to 25 mg/m². In the weekly schedule, the exposure increased proportionately with dose from 1.5 to 12 mg/m². In all 3 studies, the statistical analysis showed no significant differences of dose-normalized $AUC_{(0\text{-}48h)}$ or $AUC_{(0\text{-}t)}$, and the test of linearity applied on $AUC_{(0\text{-}48h)}$ at the first available cycle or on $AUC_{0\text{-}t}$ at Cycle 1 Day 1 against the dose could not be rejected.

Assessment of the dose proportionality was carried out on predicted C_{max} and AUC after the first administration at Cycle 1 that were estimated in the population PK analysis in the dose range of 10 to 30 mg/m² using a power model (TED6188, TED6189, TED61890, and EFC6193). In terms of C_{max}, no major deviation to the dose proportionality was observed between 10 and 30 mg/m². A 2-fold increase in dose (10 to 20 mg/m²) led to a 1.83-fold increase in C_{max} with 90% CIs of 1.48 to 2.27 and a 3-fold increase in dose (10 to 30 mg/m²) led to a 2.61-fold increase in C_{max} with 90% CIs of 1.85 to 3.67. For log-transformation of AUC, a linear trend was also observed to a certain degree. A 2-fold increase in dose (10 to 20 mg/m²) led to a 1.77-fold increase in AUC with 90% CIs of 1.61 to 1.96. A 3-fold increase in dose (10 to 30 mg/m²) led to a 2.48-fold increase in AUC with 90% CIs of 2.12 and 2.90. However, the diagnostic figures for AUC showed some deviations from the power model. Thus, the most appropriate method to assess to dose proportionality was pair-wise comparisons of dose levels using an ANOVA model. Pair-wise comparisons between the AUC at 10 mg/m² *versus* 20 and 25 mg/m² (N>10 for each dose level) were undertaken using a fixed effects model. A proportional increase in AUC was observed between 10 and 20 mg/m² and between 10 and 25 mg/m² with a nearly perfect 1.95-fold increase in AUC for a 2-fold increase in dose (90% CIs: 1.62 to 2.34) between 10 and 20 mg/m² and with a 2.45-fold increase in AUC for a 2.5-fold increase in dose (90% CIs: 2.11 to 2.84) between 10 and 25 mg/m².

Special populations

Results of the population pharmacokinetic model indicated that Interindividual variability of Cabazitaxel clearance was significantly related to body surface area and tumour type.

Elderly
In the population pharmacokinetic analysis in 70 patients of 65 years and older (57 from 65 to 75 and 13 patients above 75), no age effect on the pharmacokinetics of cabazitaxel was observed.

Paediatric patients
Safety and effectiveness of JEVTANA have not been established in children and adolescents below 18 years of age.

Hepatic impairment
No formal studies in patients with hepatic impairment have been conducted. However, as cabazitaxel is eliminated primarily via metabolism, increased exposure may be expected.

Renal impairment
Cabazitaxel is minimally excreted via the kidney (2.3% of the dose). No formal pharmacokinetic studies were conducted with cabazitaxel in patients with renal impairment. However, the population pharmacokinetic analysis carried out in 170 patients that included 14 patients with moderate renal impairment (creatinine clearance in the range of 30 to 50 ml/min) and 59 patients with mild renal impairment (creatinine clearance in the range of 50 to 80 ml/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel.

Pharmacokinetic interaction studies

In vitro

Cabazitaxel is mainly metabolised by CYP3A (80% to 90%). No induction potential of cabazitaxel was observed *in vitro* with human hepatocytes in primary culture for CYP1A, CYP2C9, or CYP3A. However, cabazitaxel had potential to inhibit CYP3A enzymes ([I]/Ki = 0,15), indicating a possible risk of interaction with CYP3A substrate *in vivo*, but not with other CYPs, at the intended therapeutic dose of 25 mg/m². Consequently, *in vivo* interactions with CYP3A-sensitive substrates are possible, but are unlikely for the others CYPs. I*n vitro* studies assessing the effect of potent CYP3A4 inhibitors and inducers on cabazitaxel plasmatic exposure have not been performed whereas they would have allowed estimating the magnitude of the interaction in the absence of clinical data.
In addition, at the dose of 25 mg/m², cabazitaxel seems to be a P-gp substrate but neither a P-gp inhibitor nor a BCRP, or MRP-mediated transport inhibitor. Therefore, in vivo interactions with digoxin, other P-gp substrates, or BCRP or MRP substrates are not expected *in vivo* at the dose of 25 mg/m².
As regards MRP1, MRP2 and BCRP, results show that cabazitaxel is neither a substrate nor an inhibitor of such transporters. However, this study was performed with a single cell model. Considering the low specificity of the model used in the study TRE0012, a second experiment with a different model will be performed by the applicant (see section 2.7).
In addition, in order to further investigate the disposition of cabazitaxel and the potential for metabolic and transporter-mediated interactions with other drugs, an in vitro study will be conducted to assess whether cabazitaxel is a potential substrate and/or inhibitor of liver uptake transporters (OATP1B3, OCT1 or OATP1B1) (see section 2.7).

Other in vitro data

The lack of cabazitaxel CYP2C9 inhibitory potency had been confirmed through a study performed with warfarin. According to the results of this experiment, cabazitaxel did not inhibit in vitro the major biotransformation pathway of warfarin into 7-hydroxy-warfarin, since the inhibition never reached 50% at concentrations much higher than those observed in clinical studies (up to 100 µmol/L [83 600 ng/mL]). Therefore, in vivo, warfarin hepatic metabolism should not be altered by cabazitaxel.
Effect of acetaminophen, dexamethasone, dexchlorpheniramine, dextropropoxyphen, granisetron, methylprednisolone, morphine, omeprazole, ondansetron, ranitidine, and warfarin on cabazitaxel metabolism in human liver microsomes has been also assessed since these drugs are often co-administered to the target population. Results showed that these drugs are not expected to alter cabazitaxel oxidation in vivo, at the therapeutic concentrations.

In vivo

Effects of other drugs on the pharmacokinetics of cabazitaxel

Since cabazitaxel is mainly metabolised by CYP3A (80% to 90%), potent CYP3A inhibitors and inducers may affect its pharmacokinetics in vivo. At the time of the dossier cut-off date, no specific clinical studies have been carried out to assess the effect of inhibitors or inducers of CYP3A on the pharmacokinetics of cabazitaxel.

The effect of weak CYP3A inducers (eg, prednisone/prednisolone) has been evaluated in the population pharmacokinetic analysis. Results show that prednisone/prednisolone did not significantly influence cabazitaxel clearance. As regards prednisone/prednisolone combination with cabazitaxel, data should be interpreted with caution since no usual pharmacokinetic study has been performed.
Currently, drug interaction studies and pharmacokinetic analyses are being performed with Cabazitaxel and aprepitant (a moderate CYP3A inhibitor), as part of the ongoing TCD10870 study. According to the applicant, the study is being amended to add two cohorts at the recommended dose for the combination to assess (1) the effect of ketoconazole (a strong CYP3A inhibitor) and (2) the effect of rifampicin (a strong CYP3A inducer).

Effect of cabazitaxel on the pharmacokinetics of other drugs

At time of the dossier cut-off date, no specific studies have been performed to investigate the impact of cabazitaxel on CYP3A sensitive substrates. *In vitro*, cabazitaxel inhibits CYP3A with a constant of inhibition (Ki) of 1.99 µM. Based on the C_{max} value of 0.299 µM [250 ng/ml] observed in 29 patients treated at 25 mg/m² every 3 weeks in the Phase 3 study EFC6193, the [I]/Ki value is 0.15 for CYP3A and <0.1 for other tested CYPs, indicating a possible risk of interaction with CYP3A substrates *in vivo*. The risk of interaction with the other CYP isoenzymes is unlikely.

In addition, the potential inhibitory effect of cabazitaxel on a probe CYP3A substrate (oral midazolam) will be investigated in a cohort of patients with normal hepatic function following an amendment to study POP6792. (see section 2.7 and RMP).
As a precautionary measure and before getting these key results, it is stated in the sections 4.5 and 5.2 of the SmPC that potent CYP3A inductor or inhibitor could affect the concentrations of cabazitaxel. Also, co-administration of cabazitaxel with drugs highly metabolised through CYP3A may increase the exposure of these drugs.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action of cabazitaxel were submitted.

Primary and Secondary pharmacology

The Pharmacodynamic properties of cabazitaxel were investigated during the Phase 1 studies in patients with solid tumours, in phase 2 study-ARD6191 in patient with metastatic breast cancer and in phase III study-EFC6193 in patients with hormone refractory metastatic prostate cancer. Data from 2 phase 1 studies (TED6188 and TED6190), 1 phase 2 study (ARD6191) and 1 phase 3 (EFC6193/TROPIC) study were combined for a PK/PD analysis referenced POH0258. Doses ranged from 10 to 30 mg/m². Data taken from 145 patients were available for the analysis. The PK/PD analysis attempted to correlate PK parameters (independent variables) with both activity and safety parameters (dependent variables). Overall survival was selected as the pharmacological activity endpoint in this PK/PD analysis. Only data from patients with hormone refractory prostate cancer were considered in the PK/pharmacological activity analysis since this was the target indication of interest.
In the subset of 67 hormone refractory prostate cancer patients from EFC6193, none of the PK parameters had a statistically significant association with overall survival (OS) (data not shown).

2.4.4. Discussion on clinical pharmacology

Human pharmacokinetics of cabazitaxel have been investigated during the Phase 1 studies in patients with solid tumours, in phase 2 study-ARD6191 in patient with metastatic breast cancer and in phase 3 study-EFC6193 in patients with hormone refractory metastatic prostate cancer. Data from 2 phase 1 studies (TED6188 and TED6190), 1 phase 2 study (ARD6191) and the pivotal phase 3 study (EFC6193/TROPIC) were combined for a PK/PD analysis referenced POH0258. There was no phase I study specific to prostate cancer. Pharmacokinetic data in this patient population are only taken from the pivotal phase 3 study.
Doses ranged from 10 to 30 mg/m². A total of 145 patients with pharmacokinetic parameters from the first cycle were available for the analysis. Bioanalytical studies were associated with clinical

pharmacology studies and efficacy/safety clinical studies. All methods were found to be suitable for quantitative analysis of cabazitaxel and its metabolites.
Results taken from study TED 6188 indicated that cabazitaxel exhibited a high CL representing approximately 88% of the hepatic blood flow, a large distribution within the body and a long terminal half-life. The PK were time independent up to 3 consecutive chemotherapy cycles. The PK analysis showed a dose proportional increase in $AUC_{(0\text{-}48h)}$ over the dose range tested. This finding indicated that the PK of cabazitaxel following a 1-hour i.v. infusion were linear over 10-30 mg/m². Similar results could be found in study TED 6190.
Cabazitaxel is extensively metabolised in the liver (>95%), mainly by the CYP3A4 isoenzyme (80% to 90%). Cabazitaxel is the main circulating compound in human plasma. Seven metabolites were detected in plasma (including 3 active metabolites issued form O-demethylations), with the main one accounting for 5% of parent exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and faeces.
A population pharmacokinetic model was developed and validated with data from 170 patients treated with cabazitaxel included in five studies. The main objective of this analysis was to develop and qualify a PopPK model for cabazitaxel administered in several studies performed in patients with advanced solid tumours and to investigate the influence of key demographic parameters (e.g. body surface area, age, etc.), renal function (measured by creatinine clearance) and hepatic function (measured by bilirubin, ALT, AST, and ALK), disease status (tumour type) and concomitant medication (CYP inducers). Results indicated that Interindividual variability of cabazitaxel clearance was significantly related to body surface area and tumour type.

Finally, *in vitro* studies have shown that cabazitaxel is mainly metabolised through CYP3A and inhibits CYP3A. Therefore, the metabolism of cabazitaxel may be modified by the concomitant administration of compounds which are known to be potent inhibitors (e.g., ketoconazole) or inducers (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) of CYP3A. Likewise coadministration of cabazitaxel with medicinal products that are known to be primarily metabolised through CYP3A may increase the exposure of these medicinal products. However, there is no potential risk of inhibition of medicinal products that are substrates of other CYP enzymes (1A2, 2B6, 2C9, 2C8, 2C19, 2E1, and 2D6) as well as no potential risk of induction by cabazitaxel on medicinal products that are substrates of CYP1A, CYP2C9, and CYP3A. Cabazitaxel did not inhibit *in vitro* the major biotransformation pathway of warfarin into 7-hydroxywarfarin, which is mediated by CYP2C9. Therefore, no pharmacokinetic interaction of cabazitaxel on warfarin is expected *in vivo*.

Cabazitaxel is mainly metabolised by CYP3A4 and CYP3A5 (contribution of CYP3A estimated to range from 80 to 90%) and to a lesser extent by CYP2C8. Cabazitaxel is also a substrate of P-gp.
CYP3A4, CYP3A5 and P-gp are subject to genetic polymorphism however it is not expected to play a major role in the observed variability of PK parameters of cabazitaxel. Exploratory investigations of the relationship between allelic variants of drug metabolism enzymes or transporters with PK parameters (e.g., CL, Vss) of cabazitaxel will be performed by the applicant (see section 2.7).

2.4.5. Conclusions on clinical pharmacology

The PK analysis showed a dose proportional increase in $AUC_{(0\text{-}48h)}$ over the dose range tested. This finding indicated that the PK of cabazitaxel following a 1-hour i.v. infusion were linear over 10-30 mg/m².
Results of a population pharmacokinetic model (developed and validated with data from 170 patients treated with cabazitaxel included in five studies) indicated that Interindividual variability of cabazitaxel clearance was significantly related to body surface area and tumour type.
Cabazitaxel is mainly metabolised through CYP3A and inhibits CYP3A. Therefore, its metabolism may be modified by the concomitant administration of compounds which are known to be potent inhibitors or inducers of CYP3A. Likewise, co-administration of cabazitaxel with products metabolised through CYP3A could increase the exposure of these medicinal products.

2.5. Clinical efficacy

The Applicant has provided results mainly taken from one single pivotal study EFC6193 (TROPIC). Two supportive studies are also submitted, both performed in metastatic breast cancer (MBC) patients: (i) A phase 2 study in taxoid resistant MBC patients (study ARD6191), and (ii) A dose-escalating study in association with capecitabine (Xeloda®) in second line MBC patients, after anthracycline and taxane therapy (study TCD6945).

Table 13: Description of the clinical studies provided by the Applicant

Study	Description	N (patients recruited)
EFC6193 (TROPIC)	Multicenter, multi-national, randomized, open-label phase III study comparing the efficacy and safety of cabazitaxel plus prednisone (or prednisolone) *versus* mitoxantrone plus prednisone (or prednisolone), in patients with hormone refractory metastatic prostate cancer (HRPC) previously treated with a Taxotere (or docetaxel)-containing regimen.	755
ARD6191	Multicenter, multinational, open-label, non-randomized, stratified 2-step phase II study. Taxoid resistant MBC patients were randomized within 4 PK sampling schedules (ratio 1:1:1:1).	71
TCD6945	Multicenter, dose-escalating, single arm, open-label study in MBC patients with disease progression after anthracycline and taxane therapy, in association with Capecitabine (Xeloda).	34

2.5.1. Dose response study(ies)

Two Phase 1 studies were conducted using the every 3 week schedule of administration of cabazitaxel. In one study (TED6188) the dose of 20 mg/m² administered every 3 weeks as a 1-hour intravenous (IV) infusion was established as the recommended dose while in the second study (TED6190), 25 mg/m² administered every 3 weeks as a 1-hour IV infusion was established as the recommended dose. Consequently, the dose of 20 mg/m² administered every 3 weeks as a 1-hour IV infusion was selected initially for further clinical development. The dose limiting toxicity (DLT) of cabazitaxel was neutropenia and its infectious complications at the highest dose tested, 30 mg/m² in TED6188 and 25 mg/m² in TED6190. The maximally tolerated dose (MTD) was 25 mg/m² in TED6190.
In a Phase 2 study with metastatic breast cancer patients (Study ARD6191), the safety and anti-tumour activity was assessed at the dose of 20 mg/m² every 3 weeks at the first cycle, with possible intra-patient escalation to 25 mg/m2 at Cycle 2 allowed in the absence of any toxicity Grade >2 at Cycle 1. In 21 patients out of 71 patients, the dose of cabazitaxel could be escalated to 25 mg/m2 IV after the first cycle.
The 25 mg/m² dose was chosen for the main study (EFC 6193) because it was expected to provide optimal dose intensity and potentially increased clinical benefit.

2.5.2. Main study

TROPIC Study (EFC 6193)

The TROPIC Study was a multicenter, multi-national, randomised, open-label phase 3 study comparing the efficacy and safety of cabazitaxel plus prednisone or prednisolone *versus* mitoxantrone plus prednisone or prednisolone, in patients with metastatic HRPC previously treated with a docetaxel-containing regimen.

Methods

Study Participants

Inclusion and exclusion criteria

Main inclusion and exclusion criteria are described in the following table:

Table 14: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Histologically or cytologically proven prostate adenocarcinoma, refractory to hormone therapy and previously treated with a docetaxel-containing regimen. Either : – measurable disease : documented progression of disease by RECIST criteria (at least 1 visceral or soft tissue metastatic lesion), measuring at least 10 mm in the longest diameter (or two times the slice thickness) on spiral CT scan or MRI (chest, abdomen, pelvis) or 20 mm on conventional CT or chest X-ray for biopsy proven, clearly defined lung lesion surrounded by aerated lung. Previously irradiated lesions, primary prostate lesion, and bone lesions were considered non-measurable disease. – non-measurable disease: documented rising PSA levels or appearance of new lesion. Rising PSA was defined as at least two consecutive rises in PSA to be documented over a reference value [measure 1] taken at least one week apart. A third or a fourth confirmatory PSA measure was required, within 4 weeks prior to randomisation, [second beyond the reference level] to be greater than the second measure and it was to be obtained at least 7 days after the second measure. Prior castration by orchiectomy and/or LH-RH agonist with or without anti-androgen, anti-androgen withdrawal, monotherapy with estramustine, or other hormonal agents. Life expectancy >2 months Eastern Cooperative Oncology Group performance status (PS) 0 to 2. Age ≥18 years.	- Previous treatment with mitoxantrone. - Previous treatment with <225 mg/m² cumulative dose of docetaxel. - Prior radiotherapy to ≥40% of bone marrow. Prior treatment with one dose of a bone-seeking radio-isotope within less than 8 weeks (samarium-153 or P-32) and less than 12 weeks (strontium-89). - Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrolment. - Active Grade ≥2 peripheral neuropathy. - Active Grade ≥2 stomatitis. - Active secondary cancer including prior malignancy from which the patient had beendisease-free for ≤5 years. - Known brain or leptomeningeal involvement - History of severe hypersensitivity reaction (≥Grade 3) to polysorbate 80 containing drugs. - History of severe hypersensitivity reaction (≥Grade 3) or intolerance to prednisone. - Other concurrent serious illness or medical conditions - Inadequate organ function as evidenced by the following peripheral blood counts, and serum chemistries at enrollment: – Neutrophils ≤1.5 x 109/L – Hemoglobin ≤10 g/dL – Platelets ≤100 x 109/L – Total bilirubin ≥ upper limit of normal (ULN) – Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) ≥1.5 x ULN – Alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT) ≥1.5 x ULN – Creatinine ≥1.5 x ULN - Uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension. History of congestive heart failure, or myocardial infarction within last 6 months was also not allowed. - Left ventricular ejection fraction ≤50% by multi-gated radionuclide angiography (MUGA) scan or echocardiogram - Uncontrolled diabetes mellitus - Active uncontrolled gastroesophageal reflux disease (GERD) - Active infection requiring systemic antibiotic or anti-fungal medication - Participation in another clinical trial with any investigational drug within 30 days prior to study enrollment. - Concurrent or planned treatment with strong inhibitors of cytochrome P450 3A4/5. A 1-week washout period was necessary for patients who were already on these treatments.

Treatments

Randomised study medications were:

- **Cabazitaxel** was administered intravenously, over 1 hour every 3 weeks, at a starting dose of 25 mg/m².
- **Mitoxantrone** was administered intravenously, over 15 to 30 minutes every 3 weeks, at a starting dose of 12 mg/m².

Prednisone or prednisolone, 10 mg, was administered orally, daily, to all patients.

The study allowed for one dose reduction for toxicity (from 25 mg/m² to 20 mg/m² for cabazitaxel, and from 12 mg/m² to 10 mg/m² for mitoxantrone). No dose escalation is mentioned in the protocol.

Premedication in the cabazitaxel group included an antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or other antihistamine), steroid (dexamethasone 8 mg or equivalent steroid), and H2 antagonist (ranitidine or other H2 antagonist with the exception of cimetidine).

Concomitant therapy with agents known to have anti-cancer activity was not permitted during the treatment phase of the study. Treatment with radiotherapy, hormones, or chemotherapeutic agents was also not permitted; with the exception of the following:

LH-RH agonists that were ongoing prior to study entry, the steroids given for new adrenal failure, and the hormones administered for non-disease related conditions.

The use of bisphosphonates was allowed. However, this dose had to be stable for 12 weeks prior to the enrolment and during the study treatment period. In addition, the patients who were treated with LH-RH agonists continued their therapy during the study treatment period.

Withdrawal, Removal and Replacement of patients

Treatment with study medication was discontinued if it was considered to be in the best interest of the patient. Reasons for treatment discontinuation included:

- Disease progression (or death due to progressive disease [PD]) ;
- Adverse event (including death), treatment-limiting toxicity, intercurrent medical problem, that contra-indicate continuation of anti-cancer chemotherapy ;
- Voluntary withdrawal ;
- Poor compliance ;
- Patients discontinued the study medication if they completed 10 cycles of treatment.

Patient lost to follow-up were withdrawn from the trial.

Objectives

The **primary objective** of this study was to determine whether cabazitaxel in combination with prednisone (prednisolone) improves Overall Survival (OS) when compared to mitoxantrone in combination with prednisone (prednisolone).

Secondary objectives were to compare the progression free survival, overall response rate (ORR), PSA progression, PSA response, pain progression and pain response, as well as assess the safety and pharmacokinetics of cabazitaxel.

Outcomes/endpoints

The primary efficacy endpoint was OS, defined as the time interval from the date of randomisation to the date of death due to any cause.

Other endpoints:

Progression free survival (PFS) was defined as the time between randomisation and the date of progression (PSA progression, tumour progression, or pain progression) or date of death due to any cause, whichever occurred first.

Objective response (complete and partial response: CR and PR) for measurable disease were assessed by investigators according to RECIST criteria.

Pain Response was defined as a 2-point or greater reduction from baseline median present pain intensity (PPI) with no concomitant increase in analgesic score (AS), or reduction of at least 50% in analgesic use from baseline mean AS (only in patients with baseline mean AS ≥10) with no concomitant increase in pain, for two consecutive evaluations at least 3 weeks apart.

Pain Progression was defined as an increase of ≥1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits or 5% increase in the mean analgesic score compared with the baseline score and noted on two consecutive three-week-apart visits OR requirement for local palliative radiotherapy.

Time to tumour progression (TTP) was added as a secondary efficacy endpoint in the efficacy analyses. It was defined as the number of months from the date of randomisation to evidence of PD based upon tumour measurements (RECIST criteria). Patients without PD were censored at their last tumour assessment.

Sample size

According to the following statistical assumptions for sample size calculation, a total of 720 patients were to be enrolled to observe a specified number of 511 deaths:

- 2-sided 5% alpha level
- Statistical power for overall survival: 90%
- Hazard ratio [M+P/(C+P)]: 1,25
- Median survival for the mitoxantrone + prednisone arm: 8 months
- Patient accrual: 24 months
- Follow-up period 24 months
- Time to 50% accrual: 15.6 months
- Randomisation: 1:1 [M+P:C+P]

Randomisation

The randomisation procedure was designed according to the 2 stratification factors:

- Measurability of disease per RECIST criteria (measurable *versus* non-measurable disease),
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 *versus* 2),

and used a dynamic allocation method.

Blinding (masking)

This study was an open-label study. The Sponsor's clinical team was blinded to treatment assignments. A Steering Committee and Independent Data Monitoring Committee (IDMC) were in place to closely monitor the data and study conduct. An external contract statistician independent from the Sponsor provided unblinded results to the IDMC.

Statistical methods

Efficacy analyses

Time-to-event data were analysed using the Kaplan-Meier method. A stratified Log-rank test was used to compare time-to-event distributions, and adjusted hazard ratios were calculated using stratified Cox proportional hazards models.

Safety analysis was performed on all patients who received at least part of one dose of study drug.

One pre-planed futility analysis (interim analysis) was performed on the PFS endpoint at the time of 225 PFS events.

A second interim analysis "for efficacy" was planned in an amended protocol to be performed on the primary endpoint OS at the time of 307 deaths (60% of the 511 deaths expected). Statistical

significance level was consequently adjusted using the O'Brien-Fleming Type I error spending function (0.0076 at the second interim analysis, and 0.0476 at the final analysis). Actually, the IDMC reviewed the second interim analysis in June 2009 (365 deaths); thus, the statistical significance level at this interim analysis was 0.0160 since the analysis was done with 365 deaths instead of the planned 307 deaths. At the final analysis, this statistical significance level became 0.0452.

Handling for missing data

No imputation of missing data was performed. A sensitivity analysis was done to assess the effect of missing data (delayed or skipped visits) on efficacy endpoints.

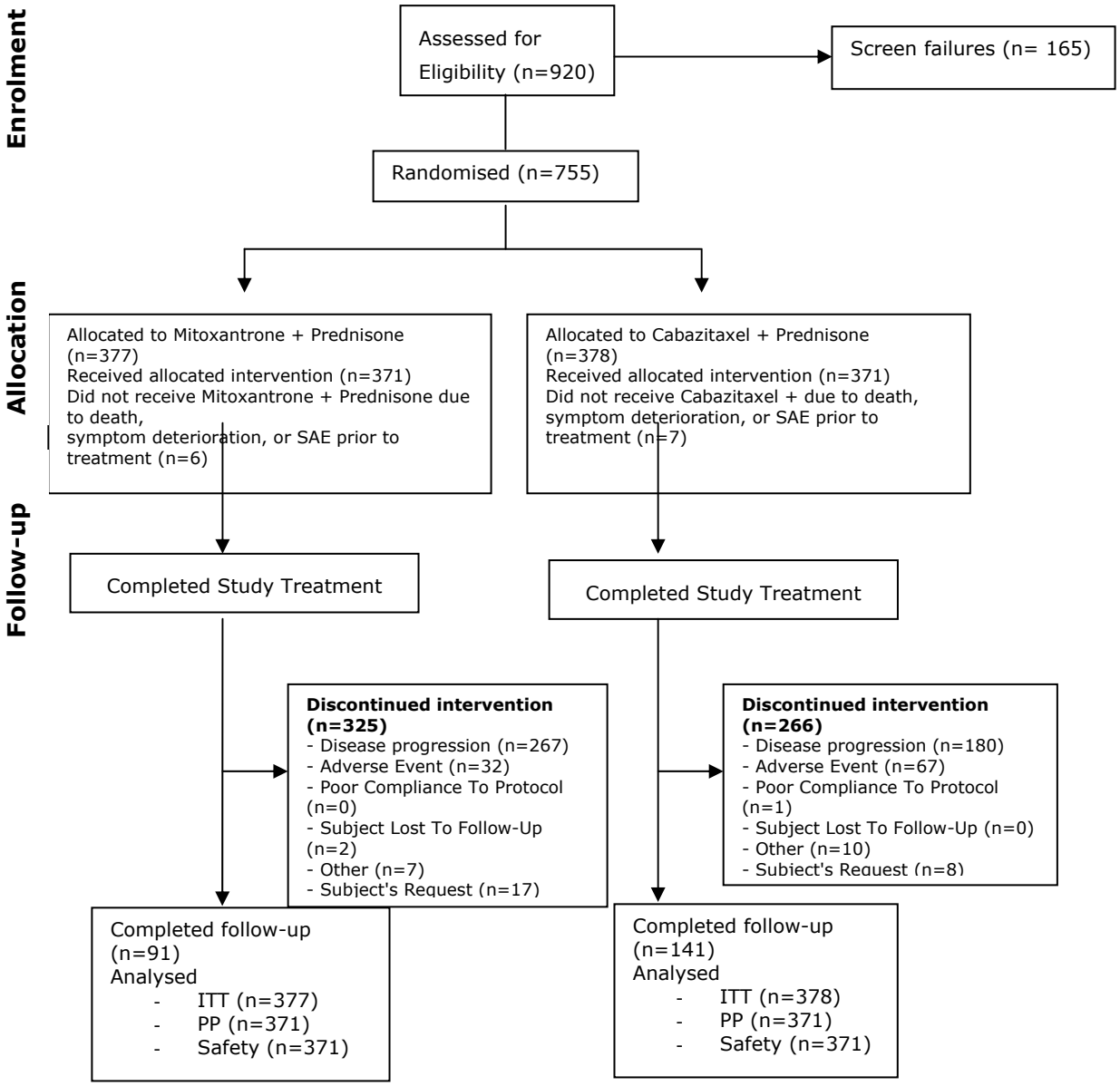
Subgroups analyses

The following prognostic factors were considered in the subgroup analyses for overall survival: ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, country, pain at baseline, PSA status, time from last docetaxel to randomisation, docetaxel dose, and time of progression from last docetaxel.

Additional analyses were performed in efficacy subgroups with a hazard ratio of 1. Overall survival was secondary analysed by baseline liver tests results, using a Cox proportional hazards model with 2 covariates (treatment effect and liver function effect).

Results

Participant flow



Recruitment

A total of 755 patients were randomised into the study, 378 in the Cabazitaxel + prednisone group and, 377 in the mitoxantrone + prednisone group, consistent with the planned 1:1 randomisation. Only 13 patients, 6 (1.6%) in the mitoxantrone and 7 (1.9%) in the cabazitaxel group, failed to received a single dose of study drug. Thus, the safety population was comprised of 742 patients (371 in each group).

Patients were censored in both arms (98 in the cabazitaxel group, 144 in the mitoxantrone group) at the study cut-off aimed at reaching 511 deaths on 25 September 2009. Among them, 3 patients in the cabazitaxel group and 7 patients in the mitoxantrone group were lost to follow up before the study cut-off date.

As of the 25 September 2009 cut-off date for final analysis on OS, 232 patients (31%) completed follow-up, 91 (24%) in the mitoxantrone group and 141 (37%) in the Cabazitaxel group.

The most frequent primary reason for treatment discontinuation was progressive disease, 180 patients (47.6%) in the Cabazitaxel group and 267 patients (70.8%) in the mitoxantrone group. Treatment discontinuation due to an adverse reaction occurred in 32 patients (8.5%) in the mitoxantrone group and 67 patients (17,7%) in the cabazitaxel group. Two patients discontinued study treatment due to lost to follow-up (in the mitoxantrone group).

Conduct of the study

There were 5 amendments to the protocol, of which 2 were introduced before the inclusion of any patients. Amendment 1 allowed the use of prednisolone (10 mg orally daily) in combination with cabazitaxel or mitoxantrone in those countries where prednisone was not commercially available. Amendment 4 added an exclusion criterion to exclude patients who had not received at least 3 cycles or <225 mg/m2 cumulative dose of prior docetaxel therapy and modified the definition of pain progression that pain had to be cancer-related and pain progression must have been supported by clinical and/or radiological evidence of disease progression. Accordingly, patients were to be removed from study treatment for cancer-related pain progression. Amendment 5 added one interim analysis to be performed at the time of 307 deaths (the 60% of the 511 deaths in the final analysis of the protocol) to assess the primary efficacy endpoint of OS based on the O'Brien-Fleming type I error spending function.
Major deviations to the protocol were associated with eligibility criteria (44 patients – 11.9% – in the mitoxantrone group and 40 patients – 10.8% – in the cabazitaxel group), or not having a 5 PPI score and AS at each visit (57 patients – 15.4% – in the mitoxantrone group and 49 patients – 13.2% – in the cabazitaxel group).

Two patients (one in each group) received the other treatment than that allocated. These patients were evaluated for safety based on the treatment they received. Efficacy was evaluated based on the group to which each patient was randomised.

Other deviations (dosing irregularities, missing values, concomitant medications) occurred in less than 5% of patients in either group.

Baseline data

Table 15: Summary of baseline and demographic characteristics – ITT population

	MTX+PRED (N=377)	CBZ+PRED (N=378)
Age, in years		
Median	67.0	68.0
Minimum	47	46
Maximum	89	92
Age		
18 to 64	162 (43.0%)	133 (35.2%)
65 to 74	145 (38.5%)	176 (46.6%)
75 and above	70 (18.6%)	69 (18.3%)
Race		
Caucasian/White	314 (83.3%)	317 (83.9%)
Black	20 (5.3%)	20 (5.3%)
Asian/Oriental	32 (8.5%)	26 (6.9%)
Other	11 (2.9%)	15 (4.0%)
ECOG PS		
0 or 1	344 (91.2%)	350 (92.6%)
0	120 (31.8%)	141 (37.3%)
1	224 (59.4%)	209 (55.3%)
2	33 (8.8%)	28 (7.4%)
ECG		
Normal	251 (66.6%)	268 (70.9%)
Abnormal	98 (26.0%)	86 (22.8%)
Missing	28 (7.4%)	24 (6.3%)
Echocardiography (Left ventricular ejection fraction) %		
Number of patients	243	235
Median	64.00	63.00
Minimum	42.0	38.0
Maximum	80.0	86.0
Radionuclide Ventriculography (LVEF) %		
Number of patients	129	140
Median	63.00	62.00
Minimum	50.0	50.2
Maximum	80.0	81.0
PSA (in ng/mL)		
Number of patients	370	371
Median	127.5	143.9
Minimum	2	2
Maximum	11220	7842
Measurable Disease		
Measurable Disease	204 (54.1%)	201 (53.2%)
Not Measurable Disease	173 (45.9%)	177 (46.8%)
Extent of disease		
Metastatic	356 (94.4%)	364 (96.3%)
Loco Regional Recurrence	20 (5.3%)	14 (3.7%)
Missing	1 (0.3%)	0

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

Demographics: the majority of patients were Caucasian (83.6%) and of age 65 years or older (60.9%), with ECOG performance status 0-1 (91.9%).

Prognostic Factors : a relatively small percentage of ITT patients had factors associated with poor prognosis, including CTCAE grade ≥3 haemoglobin (0.4%), ECOG performance status ≥ 2 (8.1%), and CTCAE grade ≥3 alkaline phosphatise (8.1%),

Disease diagnosis and staging prior treatment: the majority of patients had a metastatic stage disease (95.3%).

Prior anticancer therapies: almost all patients (99.3%) had received hormonal therapy for their prostate cancer, 60.1% of patients had received radiotherapy, 53.3% of the patients had prior surgery, 14.9% of the patients had received ≥2 regimen of prior docetaxel-based chemotherapy. Most of the patients (72%) progressed during of within 3 months since last docetaxel dose.

Table 16: Summary of prior anticancer therapies and procedures – number (%) of patients – ITT population

	MTX+PRED (N=377)	**CBZ+PRED (N=378)**
Prior Treatment Biological Modifiers	36 (9.5%)	26 (6.9%)
Prior Treatment Hormonal Therapy	375 (99.5%)	375 (99.2%)
Surgical	205 (54.4%)	198 (52.4%)
Radiation		
Curative	112 (29.7%)	98 (25.9%)
Palliative	110 (29.2%)	134 (35.4%)
Chemotherapy		
1 regimen	268 (71.1%)	260 (68.8%)
2 regimens	79 (21.0%)	94 (24.9%)
3 or more regimens	30 (8.0%)	24 (6.3%)

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

Table 17: Summary of Taxotere-containing regimens prior to the trial - ITT population

		MTX+PRED (N=377)	**CBZ+PRED (N=378)**
Months from last Taxotere dose to randomisation of this trial	Median	3.7	4.1
	Mean (SD)	5.7 (6.8)	6.2 (6.7)
Number of patients randomised	Within 6 months since last Taxotere dose	270 (71.6%)	234 (61.9%)
	More than 6 months since last Taxotere dose	107 (28.4%)	143 (37.8%)
	Missing	0	1 (0.3%)
Months from last Taxotere dose to progression	Median	0.7	0.8
	Mean (SD)	2.2 (4.4)	2.1 (4.4)
Number of patients progressed	During last Taxotere treatment	104 (27.6%)	115 (30.4%)
	<3 months since last Taxotere dose	181 (48.0%)	158 (41.8%)
	3 months to < 6 months after last Taxotere dose	50 (13.3%)	58 (15.3%)
	≥6 months since last Taxotere dose	40 (10.6%)	44 (11.6%)
	Missing	2 (0.5%)	3 (0.8%)
Number of regimen containing Taxotere			
	1	327 (86.7%)	316 (83.6%)
	2	43 (11.4%)	53 (14.0%)
	3 or more	7 (1.9%)	9 (2.4%)
Total prior Taxotere (mg/m²)			

	Median	529.2	576.6
	Min	0	22
	Max	2999	3089
Number of patients received total Taxotere			
	<225 mg/m²	30 (8.0%)	29 (7.7%)
	>=225 to 450 mg/m²	112 (29.7%)	94 (24.9%)
	>=450 to 675 mg/m²	105 (27.9%)	112 (29.6%)
	>=675 to 900 mg/m²	57 (15.1%)	74 (19.6%)
	>=900 mg/m²	68 (18.0%)	66 (17.5%)
	Missing	5 (1.3%)	3 (0.8%)

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

Numbers analysed

The primary analysis of the primary efficacy endpoint was performed using the ITT population. Secondary and exploratory efficacy endpoints were analysed in the ITT population, whenever applicable (table 18)

Table 18: Data sets analysed

Analysis Population	**Number (%) of Patients**		**Total**
	Mitoxantrone	**Cabazitaxel**	
Efficacy Intent-to-Treat (all randomised patients)	377 (100)	378 (100)	755 (100)
Overall response rate (patients with measurable disease)	204 (54.1)	201 (53.2)	405 (53.6)
PSA response (patients with baseline PSA>20 g/mL)	325 (86.2)	329 (87.0)	654 (86.6)
Pain response (patients with median PPI≥2 on the McGill-Melzack scale and/or a mean AS ≥10 points at baseline)	168 (44.6)	174 (46.0)	342 (45.3)
Per protocol cohort (received at least 1dose)	371 (98.4)	371 (98.4)	742 (98.3)
Safety population	371 (98.4)	371 (98.4)	742 (98.3)

Outcomes and estimation

In the **primary analysis**, the superiority of cabazitaxel as compared to mitoxantrone was demonstrated, with a 2.4 months increase of median OS, and a 30% reduction in risk of death (HR=0.70).

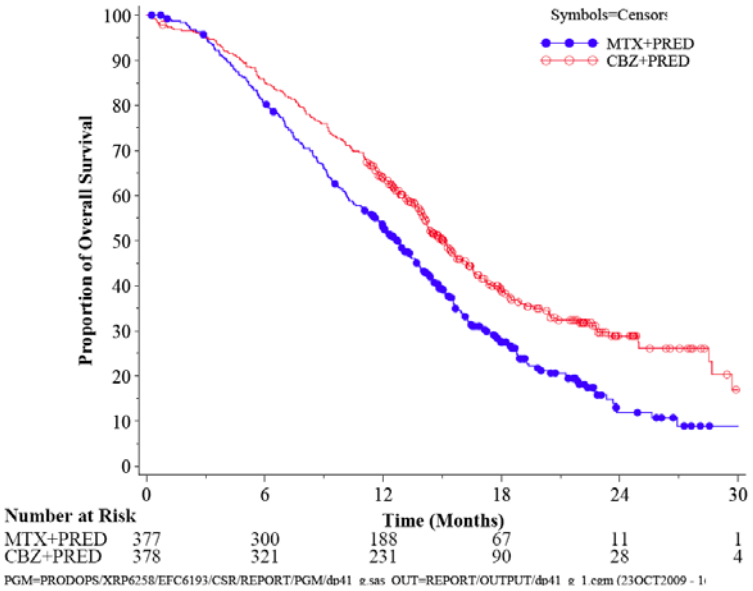


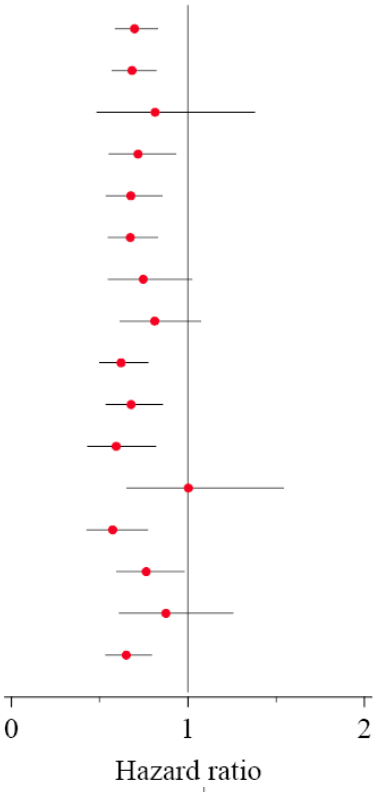
Figure 1: Overall survival - ITT population

Table 19: Primary analysis of overall survival - ITT population

	MTX + PRED (N=377)	**CBZ + PRED (N=378)**	**HR[1] (95% CI)**	**p[2]**
Number of patients with death (%)	279 (74.0)	234 (61.9)		
Median survival in months (95% CI)	**12.7** (11.6 – 13.7)	**15.1** (14.1 – 16.3)	0.70 (0.59 – 0.83)	**<0.0001**

[1]HR is estimated using a Cox proportional hazards regression model. A HR<1 indicates a lower risk of CBZ+Pred with respect to MTX+Pred.
[2]p-value from stratified log-renk test, stratifying for ECOG performance status and measurable disease at baseline.

Factor	Subgroup	Number	Hazard ratio(95% CI)
ITT population	All patients	755	0.70 (0.59 - 0.83)
ECOG Status	0,1	694	0.68 (0.57 - 0.82)
ECOG Status	2	61	0.81 (0.48 - 1.38)
Measurable disease	No	350	0.72 (0.55 - 0.93)
Measurable disease	Yes	405	0.68 (0.54 - 0.85)
No. of prior chemo	1	528	0.67 (0.55 - 0.83)
No. of prior chemo	>=2	227	0.75 (0.55 - 1.02)
Age	< 65	295	0.81 (0.61 - 1.08)
Age	>= 65	460	0.62 (0.50 - 0.78)
Country	Europe countries	402	0.68 (0.53 - 0.86)
Country	North America countries	235	0.59 (0.43 - 0.82)
Country	Other countries	118	1.00 (0.65 - 1.54)
Pain at baseline	No	314	0.57 (0.43 - 0.77)
Pain at baseline	Yes	310	0.76 (0.59 - 0.98)
Rising PSA at baseline	No	159	0.88 (0.61 - 1.26)
Rising PSA at baseline	Yes	583	0.65 (0.53 - 0.80)



ITT population	All patients	755	0.70 (0.59 - 0.83)
Last taxotere to random.	< 6 months	504	0.77 (0.63 - 0.94)
Last taxotere to random.	>= 6 months	250	0.64 (0.46 - 0.89)
Total taxotere dose	< 225 mg/m2	59	0.96 (0.49 - 1.86)
Total taxotere dose	>= 225 to 450 mg/m2	206	0.60 (0.43 - 0.84)
Total taxotere dose	>= 450 to 675 mg/m2	217	0.83 (0.60 - 1.16)
Total taxotere dose	>= 675 to 900 mg/m2	131	0.73 (0.48 - 1.10)
Total taxotere dose	>= 900 mg/m2	134	0.51 (0.33 - 0.79)
Progression	During last Taxotere treatment	219	0.65 (0.47 - 0.90)
Progression	Within first 3 months since last Taxotere dose	339	0.70 (0.55 - 0.91)
Progression	Between 4th & 6th month since last Taxotere dose	108	0.79 (0.48 - 1.28)
Progression	More than 6 months since	84	0.74 (0.39 - 1.40)

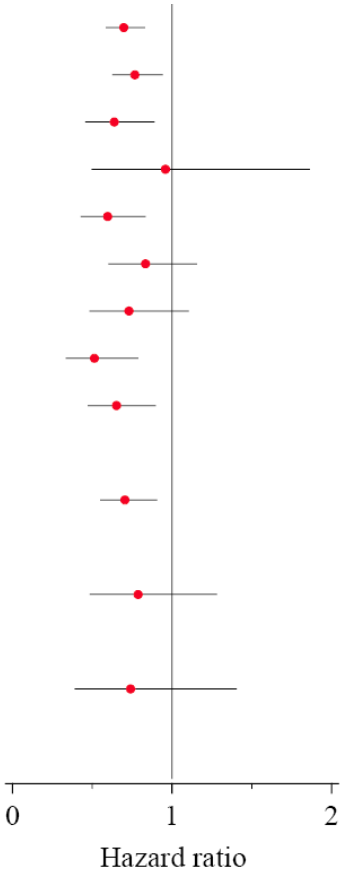


Figure 2: Hazard ratio of overall survival for potential prognostic factors - CBZ + PRED vs. MTX + PRED - ITT population

Table 20: Summary of efficacy results (hazards ratios)

	MTX + PRED (N=377)	CBZ + PRED (N=378)	HR[1] (95% CI)	P[2]
Median PFS in months (95% CI)	1.4 (1.4 – 1.7)	2.8 (2.4 – 3.0)	**0.74** (0.64 – 0.86)	**<0.0001**
Median Tumour Progression free in months (95% CI)	5.4 (4.7 – 6.5)	8.8 (7.4 – 9.6)	**0.61** (0.49 – 0.76)	**<0.0001**
Median PSA Progression free in months (95% CI)	3.1 (2.2 – 4.4)	6.4 (5.1 – 7.3)	**0.75** (0.63 – 0.90)	**0.001**
Median Pain Progression free in months (95% CI)	**-**	11.1 (8.0 – .)	**0.91** (0.69 – 1.19)	**0.52**

[1]HR is estimated using a Cox proportional hazards regression model. A HR<1 indicates a lower risk of CBZ+Pred with respect to MTX + Pred.
[2]p-value from stratified log-renk test, stratifying for ECOG performance status and measurable disease at baseline.

Table 21: Summary of efficacy results (response rates)

	MTX + PRED (N=377)	CBZ + PRED (N=378)	P[3]
Number of overall response	9 (4.4)	29 (14.4)	**0.0005**
(CR or PR) (%) and 95% CI[1]	1.6 – 7.2	9.6 – 19.3	
Number of PSA response (%)	58 (17.8)	129 (39.2)	**0.0002**
95% CI of PSA response rate [1]	13.7 – 22.0	33.9 – 44.5	
Number of pain response (%)	13 (7.7)	16 (9.2)	**0.63**
95% CI of PSA response rate[1]	3.7 – 11.8	4.9 – 13.5	

[1]estimated by Normal approximation.

[2]comparing the frequency distribution based on Chi-square test. Record with missing values for factors or response were excluded from statistical analyses.

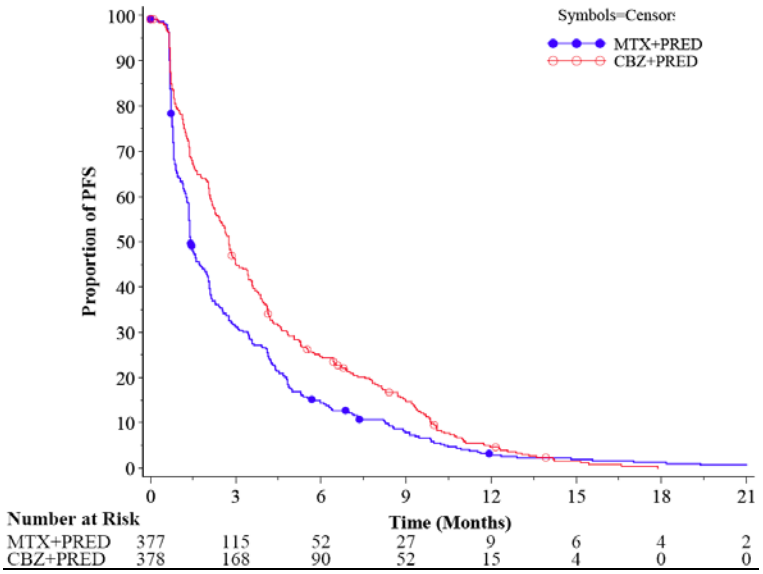


Figure 3: Kaplan-Meier curves of PFS - ITT population

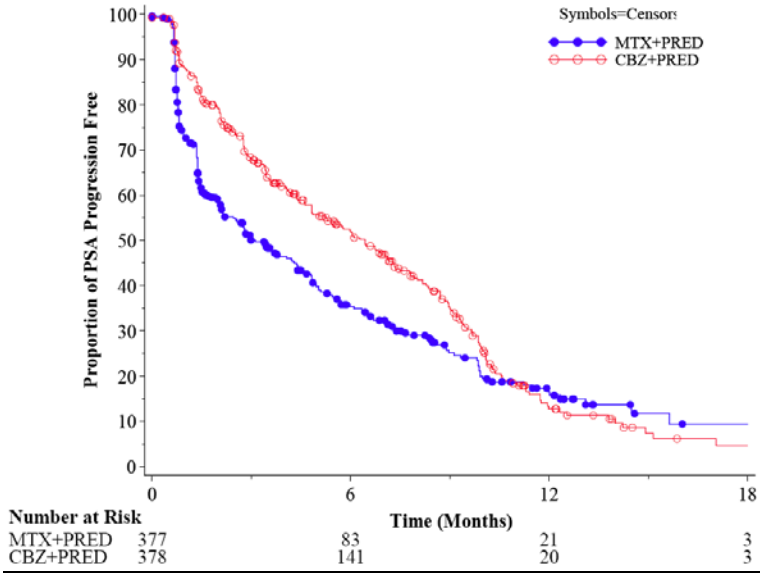


Figure 4: Kaplan-Meier curves of PSA progression - ITT population

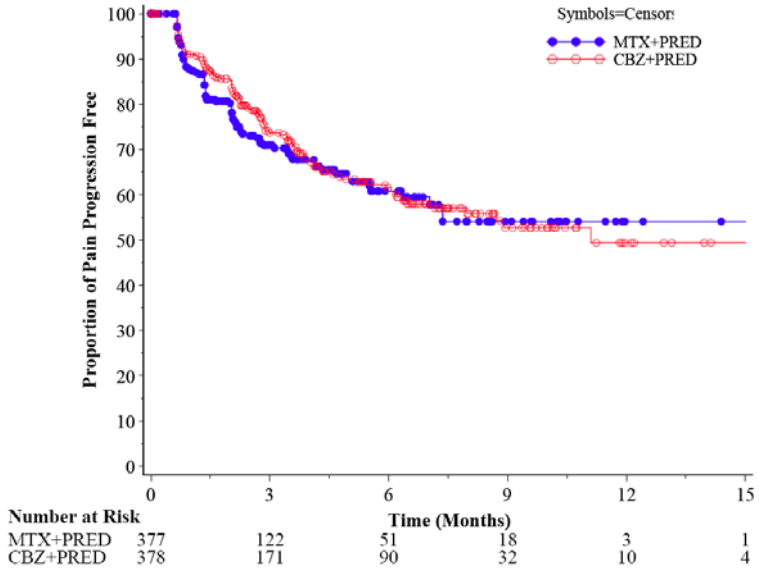


Figure 5: Kaplan-Meier curves of pain progression - ITT population

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22. Summary of Efficacy for trial EFC6193 (TROPIC)

Title: A Randomised, Open Label Multicenter Study of XRP6258 at 25 mg/m2 in Combination With Prednisone Every 3 Weeks Compared to Mitoxantrone in Combination With Prednisone for the Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere®-Containing Regimen			
Study identifier	EFC6193		
Design	Multicenter, multinational, open-label, randomised, comparative study		
	Duration of treatment: Duration of Run-in phase: Duration of Extension phase:		30 weeks not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Cabazitaxel + prednisone (CBZ + PRED)		CBZ 25 mg/m^2 IV every 3 weeks and PRED 10 mg orally given daily, 378 patients randomised
	Mitoxantrone + prednisone (MTX + PRED)		MTX 12 mg/m^2 IV every 3 weeks and PRED 10 mg orally given daily, 378 patients randomised
Endpoints and definitions	Primary endpoint	Overall survival (OS)	The primary efficacy assessment was OS defined as the time interval from the date of randomisation to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever had come first.
	Secondary endpoint	Progression free survival (PFS)	PFS was evaluated from the date of randomisation to the date of tumor progression, PSA progression, pain progression (pain progression supported by clinical evidence and/or radiological of disease progression), or death due to any cause, whichever occurred first

	Secondary endpoint	Overall Tumour response rate (ORR)	Objective responses (Complete Response [CR] and Partial Response [PR]) for measurable disease as assessed by Investigators according to RECIST criteria. The confirmation of objective responses was performed by repeat tumor imaging (CT scans, MRI, bone scans) at least 4 weeks after the first documentation of response.
	Secondary endpoint	PSA progression	PSA progression (assessed in all patients): − In PSA non-responders, the progression was defined as a ≥25% increase over nadir (provided that the increase in the absolute value PSA level was at least 5 ng/mL), confirmed by a second value with a ≥25% increase over baseline at least 1 week later. − In PSA responders and in patients not evaluable for PSA response at baseline, the progression was defined as a ≥50% increase over the nadir (provided that the increase in the absolute value PSA level was at least 5 ng/mL), confirmed by a second value at least 1 week later.
	Secondary endpoint	PSA response rate	PSA response (assessed only in patients with baseline PSA ≥20 ng/mL): Response required a PSA decrease of ≥50% confirmed by a second PSA value at least 3 weeks later. The duration of PSA response was measured from baseline to the last assessment at which the above criteria are satisfied.
Database lock	Cut-off date : 25 September 2009		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (except for ORR and PSA response rate)		
Descriptive statistics and estimate variability and Effect estimate per comparison	Treatment group	MTX + PRED	CBZ + PRED
	Number of subject	377	378
	OS No of patients with death (%)	279 (74.0)	234 (61.9)
	Median survival in months (95% CI)	12.7 (11.6 – 13.7)	15.1 (14.1 – 16.3)
	P-value (Log-rank test procedure)	<0.0001	
	Hazard Ratio (95% CI) using COX proportional hazard model	0.70 (0.59-0.83)	
	PFS No of patients with PFS events (%)	367 (97.3)	364 (96.3)
	Median progression free survival in months (95% CI)	1.4 (1.4 – 1.7)	2.8 (2.4 – 3.0)
	P-value (Log-rank test procedure)	<0.0001	
	Hazard Ratio (95% CI) using COX proportional hazard model	0.74 (0.64-0.86)	
	ORR (by RECIST) No. of patients evaluable (with measurable disease)	204	201

	Tumor response rate (%)(95% CI)	4.4 (1.6% to 7.2%)	14.4 (9.6% to 19.3%)
	P-value (Log-rank test procedure)	0.0005	
	PSA progression No. of patients with PSA progression (%)	252 (66.8	252 (66.7)
	Median time to PSA progression (months) (95% CI)	3.1 (2.2 - 4.4)	6.4 (5.1 - 7.3)
	P-value (Log-rank test procedure)	0.0010	
	Hazard Ratio (95% CI) using COX proportional hazard model	0.75 (0.63-0.90)	
	PSA response rate No. of patients evaluable (PSA ≥20 ng/mL at baseline)	325	329
	PSA response rate (%)(95% CI)	17.8 (13.7 - 22.0)	39.2 (33.9 - 44.5)
	P-value (Log-rank test procedure)	0.00052	

Supportive studies

Two supportive studies are provided by the applicant, both performed in MBC patients (data not shown).

Table 23: Description of the supportive studies provided by the Applicant

Study	Description	n
ARD6191	Multicenter, multinational, open-label, non-randomized, stratified 2-step phase II study. Taxoid resistant MBC patients were randomized within 4 PK sampling schedules (ratio 1:1:1:1).	71
TCD6945	Multicenter, dose-escalating, single arm, open-label study in MBC patients with disease progression after anthracycline and taxane therapy, in association with Capecitabine (Xeloda).	34

2.5.3. Discussion on clinical efficacy

The Applicant has mainly provided results taken from one single pivotal study (TROPIC Study)..

The TROPIC study was a multicenter, multinational, randomised, open-label phase 3 study comparing the efficacy and safety of cabazitaxel plus prednisone (or prednisolone) versus mitoxantrone plus prednisone (or prednisolone), in patients with mHRPC previously treated with a docetaxel-containing regimen.

Mitoxantrone was chosen as an active comparator. There is no consensus/approved drugs/combination therapies in second line mHRPC. This choice is however considered as acceptable by the CHMP.

The primary objective of the pivotal study was to determine whether cabazitaxel in combination with prednisone could improve overall survival when compared to mitoxantrone in combination with prednisone. Secondary objectives notably included progression free survival, overall response rate, PSA progression, PSA response, pain progression or pain response.

All baseline characteristics were well-balanced between the treatment groups.

The pivotal study met both primary and secondary endpoints with the exception of pain response. A statistically significant difference was observed in favour of cabazitaxel as compared to mitoxantrone in terms of OS, with a 2.4 months increase of median OS, and a 30% reduction in risk of death

(HR=0.70). The effect of cabazitaxel was consistent across the majority of subgroups, even if not significant in all of them.

However, in subgroup analyses (i) there was no statistically significant difference between cabazitaxel and mitoxantrone in patients who have received 3 cycles or less (225 mg/m²) of docetaxel, and (ii) the effect of cabazitaxel was less pronounced in patients who received two lines of docetaxel.

The data to support the selected posology in EFC6193 came from a very limited number of patients and there are still uncertainties regarding the rationale for the selected dose. A phase 3 study (EFC11785) is under preparation with the primary objective to demonstrate the non inferiority in term of overall survival (OS) of cabazitaxel 20 mg/m² (Arm A) *versus* cabazitaxel 25 mg/m² (Arm B) in combination with prednisone in patients with metastatic castration resistant prostate cancer previously treated with docetaxel. Approximately 1200 patients are planned to be enrolled. The applicant will submit the results of this study as reflected in section 2.7.

Conclusions on the clinical efficacy

In conclusion, the efficacy of cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with mHRPC previously treated with a docetaxel containing regimen has been established.

2.6. Clinical safety

Seven clinical studies (one pivotal and 6 supportive) including 591 patients treated with cabazitaxel were analysed for safety:

- four phase 1 studies (TED6188, TED6189, TED6190, and BEX6702) in solid tumours,
- one phase 2 study (ARD6191) in metastatic breast cancer,
- one phase 2 combination therapy study (TCD6945) in metastatic breast cancer, in combination with capecitabine,
- one phase 3, pivotal study (EFC6193) in hormone refractory prostate cancer (HRPC).

. Studies TED6188, TED6189, and TED6190 were dose-finding phase 1 studies in patients with advanced solid tumours. In addition, eight patients in phase 1 programme had a diagnosis of prostate cancer. Only one phase 3 pivotal study (EFC6193) was conducted in the requested indication.
Different doses of cabazitaxel from 10 to 30 mg/m² every 3 weeks or from 1,5 to 12 mg/m² one weekly were investigated in 99 patients in phase 1 studies.
Study BEX6702 was an open study investigating the disposition of [14C]-Cabazitaxel at 25 mg/m² administered as a 1-hour infusion every 3 weeks to 4 patients with advanced solid tumours. Study ARD6191 was a phase 2 dose-escalation study in patients with taxoid-resistant metastatic breast cancer that also compared the effects of cabazitaxel (84 patients) and larotaxel (12 patients). Study TCD6945 was a phase 2 dose-escalation (Part 1) and efficacy (Part 2) study of Cabazitaxel 20 or 25 mg/m² in combination with capecitabine (825 mg/m² and 1000 mg/m² twice daily) in 33 patients with metastatic breast cancer. Study EFC6193 was a pivotal, phase 3, open-label study in patients with metastatic HRPC, comparing 25 mg/m² of cabazitaxel in combination with prednisone or prednisolone in 371 patients and mitoxantrone in combination with prednisone or prednisolone in also 371 patients.

Two studies are ongoing:
- study TCD11068, in combination with gemcitabine administered in patients with advanced solid malignancies,
- study TCD10870, in combination with cisplatin.

Patient exposure

Overall, during the development program, a total of 591 patients who received at least one dose of Cabazitaxel in 7 clinical studies were included in the safety analysis. Among them, 371 male subjects have been exposed to Cabazitaxel at the recommended dose of 25 mg/m² in combination with prednisone or prednisolone every 3 weeks for the current MAA (see table 24). Different doses and different regimens have been studied during the development programme. Weekly administration was more harmful for treated patients than the drug administration every 3 weeks.

Table 24: Patient exposure

Open studies (indication)	Integrated group	IV Administration	Patients exposed	Patients exposed to the proposed dose range
EFC6193 (HRPC)	- 25 mg/m² Cabazitaxel/ Prednisone	Every 3 weeks	371	**371**
	- 12 mg/m² mitoxantrone/ prednisone		371	0
TED6188 (advanced solid tumors)	- 10, 20 mg/m² Cabazitaxel	Every 3 weeks	10	0
	- 25 mg/m² Cabazitaxel		6	**6**
	- 30 mg/m² Cabazitaxel		5	0
TED6189 (advanced solid tumors)	1.5, 3, 6, 8.4, 10 and 12 mg/m² Cabazitaxel	Weekly	42	0
TED6190 (advanced solid tumors)	- 10, 15, 20 mg/m²	Every 3 weeks	29	0
	- 25 mg/m² Cabazitaxel		7	**7**
ARD6191 (Taxoid-resistant MBC)	- Arm A 20 mg/m² - 25 mg/m² Cabazitaxel	- Every 3 weeks	50	0
		- Every 3 weeks	21	**21**
	- Arm B 10 mg/m²	- Weekly	13	0
	- Arm C Larotaxel		12	0
BEX6702 (advanced solid tumors)	25 mg/m² Cabazitaxel	Every 3 weeks	4	**4**
TCD6945 (MBC with disease progression)	- 20 mg/m² Cabazitaxel + capecitabine	Every 3 weeks	27	0
	- 25 mg/m² Cabazitaxel + capecitabine		6	**6**

The dose of 20 mg/m² was firstly studied as the appropriate dose but the dose of 25 mg/m² was chosen for the phase 3 pivotal study because it was expected to provide optimal dose intensity and potentially increased clinical benefit. All patients had a primary tumour diagnosis of HRPC previously treated with a docetaxel-containing regimen. The demographic characteristics of age, race, measurable disease and extent of disease, were similar in the treatment groups. Median age was 67 and 68 years old for mitoxantrone and cabazitaxel, respectively.

However, the following differences have been identified and further clarified by the applicant:

- More patients were 65 to 74 years old in cabazitaxel arm (46.6% vs. 38.5% in mitoxantrone arm). An analysis of age and treatment effect by the logistic model showed an age effect on adverse events in the 2 treatment groups and no interaction between age and treatment suggesting that the observed differences in treatment emergent adverse events (TEAEs) between the younger and the elderly patients were similar in patients receiving cabazitaxel compared with mitoxantrone.
- Regarding ECOG performance, slightly more patients has an ECOG 0 in cabazitaxel group (37% vs. 31%). ECOG 0 patients might be expected to have better outcomes. The majority of patients were ECOG 1, however, with slightly more in the comparator group. These patients are good candidates for treatment, as well. More than 90% of patients in each group were included in the ECOG PS 0-1 stratification;
- With regard to the docetaxel-containing regimens prior to the trial (ITT population), the median total prior docetaxel dose is higher in cabazitaxel arm (576.6 mg/m²) compared to mitoxantrone arm (529.2 mg/m²). It is unclear what effect this difference had .A greater (median) dose of docetaxel might represent a patient who responded to taxanes for a longer period. On the other hand, it might have also put the study participant at risk, particularly for bone marrow suppression;

- The PSA level was more increased in cabazitaxel group (143.9 ng/mL) in comparison to MTX group (127.5 ng/mL). However the difference is small and no conclusion can be drawn or prediction made;
- Concerning pre-treatment, concomitant medications with corticosteroids (dexamethasone), antihistamines, and H2 antagonists were required by protocol for premedication only in cabazitaxel group, the determining factor to this difference is the patient safety and previous experience with taxanes; antibacterials, immunostimulants, antidiarrheals, blood substitutes and perfusion solutions were used significantly more frequently in patients of cabazitaxel group compared to the comparative group. This reflects the greater number of adverse events (AEs) and their treatment in the cabazitaxel group. Furthermore, the most common reason for discontinuation was disease progression, not adverse events;
- Patients in the cabazitaxel group received a median of 6 cycles of treatment (range: 1 to 10), with a median relative dose intensity (RDI) of 96.12%, and patients in the mitoxantrone group received a median of 4 cycles of treatment (range: 1 to 10) with a median RDI of 97.25% suggesting that the planned doses were achieved in both arms. Only 13,5% of patients received a maximum of 10 cycles in comparative arm while they were 29,4% who received 10 cycles of cabazitaxel treatment. The total number of cycles administered was increased in cabazitaxel group (2251) in comparison to mitoxantrone group (1736).

Adverse events

In EFC6193 pivotal study, treatment-emergent AEs (regardless of relationship to study treatment) occurred in 95.7% of patients in the cabazitaxel group and 88.4% of patients in the mitoxantrone group. Grade ≥3 TEAEs occurred in 57.4% of patients in the cabazitaxel group and 39.4% of patients in the mitoxantrone group (see table 25).

Table 25: Summary of adverse events (TROPIC study EFC6193)

	MTX+PRED (N=371)	**CBZ+PRED (N=371)**
Patients with any TEAE	328 (88.4%)	**355 (95.7%)**
Patients with grade>=3 TEAE	146 (39.4%)	**213 (57.4%)**
Patients with any serious TEAE	77 (20.8%)	**145 (39.1%)**
Patients with any TEAE leading to permanent treatment discontinuation	31 (8.4%)	**68 (18.3%)**
Death	**275 (74,1%**)	227 (61,2%)
Patients with any TEAE leading to death	17 (4.6%)	19 (5.1%)
AEs other than disease progression	7 (1.9%)*	**18 (4.9%)**
Disease Progression reported as an AE	9 (2.4%)	1 (0.3%)
Disease Progression, Hepatic Failure	1 (0.3%)	0

The most frequent TEAEs in EFC6193 study among patients treated with cabazitaxel, were diarrhoea (46.6%), fatigue (36.7%), nausea (34.2%), vomiting (22.6%), and neutropenia (21.8%). All these TEAEs were significantly more important in cabazitaxel arm compared to mitoxantrone arm (diarrhoea 10.5%, fatigue 27.5%, nausea 22,9%, vomiting 10,2%, and neutropenia 10,8%). Febrile neutropenia occurred in 7.5% patients treated with Cabazitaxel and in only 1.5% patients with mitoxantrone.

Grade ≥3 TEAEs reported in at least 3% of patients in the cabazitaxel group were neutropenia (21.3%), febrile neutropenia (7.5%), diarrhoea (6.2%), fatigue (4.9%), asthenia (4.6%), back pain (3.8%), leucopoenia (3.8%), and anaemia (3.5%).
In the Phase 1/Phase 2 studies, the percentage of patients with TEAEs ≥Grade 3 ranged from 49.4% to 61.8%. TEAEs that were more increased in these studies compared to the pivotal study were peripheral sensory neuropathy, weight decreased, headache, pyrexia, dyspnoea, myalgia and stomatitis. Asthenia was observed in more than half patients when cabazitaxel was administered once weekly. Alopecia was observed in more than 30% of patients treated by ≥25 mg/m² cabazitaxel. Hypersensitivity or injection site reactions were observed in 4.5% of patients.

Table 26: TEAEs (all Grades and Grade ≥3) regardless of relationship to study drug by preferred term (≥5% incidence in any treatment group) - Phase 3 study EFC6193

	MTX+PRED (N=371)		CBZ+PRED (N=371)	
Preferred term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Any event	328 (88.4%)	146 (39.4%)	**355 (95.7%)**	**213 (57.4%)**
Diarrhoea	39 (10.5%)	1 (0.3%)	**173 (46.6%)**	**23 (6.2%)**
Fatigue	102 (27.5%)	11 (3.0%)	**136 (36.7%)**	**18 (4.9%)**
Nausea	85 (22.9%)	1 (0.3%)	**127 (34.2%)**	7 (1.9%)
Vomiting	38 (10.2%)	0	**84 (22.6%)**	7 (1.9%)
Neutropenia	40 (10.8%)	26 (7.0%)	**81 (21.8%)**	**79 (21.3%)**
Asthenia	46 (12.4%)	9 (2.4%)	**76 (20.5%)**	**17 (4.6%)**
Constipation	57 (15.4%)	2 (0.5%)	76 (20.5%)	4 (1.1%)
Haematuria	14 (3.8%)	2 (0.5%)	**62 (16.7%)**	7 (1.9%)
Back pain	45 (12.1%)	11 (3.0%)	60 (16.2%)	14 (3.8%)
Anorexia	39 (10.5%)	3 (0.8%)	59 (15.9%)	3 (0.8%)
Pyrexia	23 (6.2%)	1 (0.3%)	45 (12.1%)	4 (1.1%)
Dyspnoea	17 (4.6%)	3 (0.8%)	44 (11.9%)	5 (1.3%)
Abdominal pain	13 (3.5%)	0	43 (11.6%)	7 (1.9%)
Dysgeusia	15 (4.0%)	0	41 (11.1%)	0
Anaemia	20 (5.4%)	5 (1.3%)	40 (10.8%)	13 (3.5%)
Cough	22 (5.9%)	0	40 (10.8%)	0
Arthralgia	31 (8.4%)	4 (1.1%)	39 (10.5%)	4 (1.1%)
Alopecia	18 (4.9%)	0	37 (10.0%)	0
Oedema peripheral	34 (9.2%)	1 (0.3%)	34 (9.2%)	2 (0.5%)
Weight decreased	28 (7.5%)	1 (0.3%)	32 (8.6%)	0
Pain in extremity	27 (7.3%)	4 (1.1%)	30 (8.1%)	6 (1.6%)
Neuropathy peripheral	4 (1.1%)	1 (0.3%)	30 (8.1%)	2 (0.5%)
Dizziness	21 (5.7%)	2 (0.5%)	30 (8.1%)	0
Febrile neutropenia	5 (1.3%)	5 (1.3%)	**28 (7.5%)**	**28 (7.5%)**
Headache	19 (5.1%)	0	28 (7.5%)	0
Urinary tract infection	11 (3.0%)	3 (0.8%)	27 (7.3%)	4 (1.1%)
Muscle spasms	10 (2.7%)	0	27 (7.3%)	0
Dyspepsia	6 (1.6%)	0	25 (6.7%)	0
Dysuria	5 (1.3%)	0	25 (6.7%)	0
Mucosal inflammation	10 (2.7%)	1 (0.3%)	22 (5.9%)	1 (0.3%)
Leukopenia	11 (3.0%)	5 (1.3%)	20 (5.4%)	14 (3.8%)
Thrombocytopenia	10 (2.7%)	1 (0.3%)	20 (5.4%)	9 (2.4%)
Pain	18 (4.9%)	7 (1.9%)	20 (5.4%)	4 (1.1%)
Hypotension	9 (2.4%)	1 (0.3%)	20 (5.4%)	2 (0.5%)
Peripheral sensory neuropathy	5 (1.3%)	0	20 (5.4%)	1 (0.3%)
Abdominal pain upper	5 (1.3%)	0	20 (5.4%)	0
Bone pain	19 (5.1%)	9 (2.4%)	19 (5.1%)	3 (0.8%)
Musculoskeletal pain	20 (5.4%)	3 (0.8%)	18 (4.9%)	2 (0.5%)

CBZ: cabazitaxel, MTX: mitoxantrone, N: population size; PRED: prednisone/prednisolone; TEAE: treatment-emergent adverse event.

The full list of ADRs is reflected in section 4.8 of the SmPC.

TEAEs in the following SOCs were more common (≥10 percentage point difference) in the cabazitaxel group (all Grades):

- Infections and infestations (34.0% cabazitaxel, 22.6% mitoxantrone)
- Blood and lymphatic system disorders predominantly due to myelosuppression (35.3% cabazitaxel, 18.1% mitoxantrone)
- Nervous system disorders (41.2% cabazitaxel, 22.4% mitoxantrone)
- Respiratory, thoracic and mediastinal disorders (27.0% cabazitaxel, 16.2% mitoxantrone)
- Gastrointestinal disorders (73.3% cabazitaxel, 48.0% mitoxantrone)
- Renal and urinary disorders (30.7% cabazitaxel, 11.3% mitoxantrone)
- General disorders and administration site conditions, primarily asthenia and fatigue (68.5% cabazitaxel, 50.1% mitoxantrone)

Table 27: Number (%) of patients with TEAE in terms of the incident rate of system organ class and high level group term >1% in Cabazitaxel group – Phase 3 study EFC6193

Primary System Organ Class High Level Grouped Term	MTX+PRED (N=371)		CBZ+PRED (N=371)	
	All grade	**Grade >=3**	**All grade**	**Grade >=3**
Any Class	328 (88.4%)	146 (39.4%)	355 (95.7%)	213 (57.4%)
Infections And Infestations	84 (22.6%)	19 (5.1%)	**126 (34.0%)**	**38 (10.2%)**
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	10 (2.7%)	6 (1.6%)	7 (1.9%)	6 (1.6%)
Blood And Lymphatic System Disorders	67 (18.1%)	38 (10.2%)	**131 (35.3%)**	**113 (30.5%)**
Immune System Disorders	3 (0.8%)	0	8 (2.2%)	1 (0.3%)
Endocrine Disorders	1 (0.3%)	0	4 (1.1%)	0
Metabolism And Nutrition Disorders	59 (15.9%)	8 (2.2%)	88 (23.7%)	**18 (4.9%)**
Psychiatric Disorders	39 (10.5%)	3 (0.8%)	46 (12.4%)	3 (0.8%)
Nervous System Disorders	83 (22.4%)	14 (3.8%)	**153 (41.2%)**	**18 (4.9%)**
Eye Disorders	16 (4.3%)	1 (0.3)	26 (7.0%)	0
Cardiac Disorders	17 (4.6%)	3 (0.8%)	25 (6.7%)	7 (1.9%)
Ear And Labyrinth Disorders	7 (1.9%)	1 (0.3%)	13 (3.5%)	0
Vascular Disorders	30 (8.1%)	7 (1.9%)	45 (12.1%)	12 (3.2%)
Respiratory, Thoracic And Mediastinal Disorders	60 (16.2%)	13 (3.5%)	**100 (27.0%)**	**19 (5.1%)**
Gastrointestinal Disorders	178 (48.0%)	6 (1.6%)	**272 (73.3%)**	**46 (12.4%)**
Hepatobiliary Disorders	6 (1.6%)	1 (0.3%)	5 (1.3%)	4 (1.1%)
Skin And Subcutaneous Tissue Disorders	61 (16.4%)	1 (0.3%)	**81 (21.8%)**	0
Musculoskeletal And Connective Tissue Disorders	148 (39.9%)	35 (9.4%)	161 (43.4%)	30 (8.1%)
Renal And Urinary Disorders	42 (11.3%)	9 (2.4%)	**114 (30.7%)**	**32 (8.6%)**
Reproductive System And Breast Disorders	9 (2.4%)	0	**17 (4.6%)**	2 (0.5%)
General Disorders And Administration Site Conditions	186 (50.1%)	36 (9.7%)	**254 (68.5%)**	**50 (13.5%)**
Investigations	50 (13.5%)	5 (1.3%)	54 (14.6%)	5 (1.3%)
Injury, Poisoning And Procedural Complications	22 (5.9%)	6 (1.6%)	22 (5.9%)	5 (1.3%)

A risk ratio of ≥2 between the cabazitaxel and mitoxantrone treatment groups was determined for the following AEs: peripheral neuropathy, febrile neutropenia, dysuria, hematuria, diarrhoea, abdominal pain, dysgeusia, dyspnea, vomiting, anemia, alopecia, neutropenia, dyspepsia, peripheral sensory neuropathy, muscle spasms, urinary tract infection, hypotension, mucosal inflammation, and thrombocytopenia. In addition, when peripheral neuropathy is considered, patient with worst grade HLT peripheral neuropathy (which includes sensitive, motor and peripheral) is 13.5% in the Cabazitaxel arm compared to 3.2 % in mitoxantrone arm. However, the majority of these events were Grade 1 and 2.

Haematological toxicity:

Twice as much anaemias, thrombocytopenias and neutropenia have been reported during the pivotal study in cabazitaxel arm (10.8%, 5.4% and 28%) in comparison to mitoxantrone arm (5.4%, 2.7% and 11.9%). Grade ≥3 neutropenia was even thrice as much with cabazitaxel compared to mitoxantrone treatment (27.5% *vs.* 8.4%). There were notably more febrile neutropenia in Cabazitaxel group (7.5% *vs.* 1.3%). Nine patients (2.4%) discontinued the cabazitaxel treatment due to Grade ≥3 neutropenia and 3 patients more due to febrile neutropenia in the pivotal study compared to zero patient in comparative arm. In addition, infections were more frequent in the cabazitaxel-treated arm compared to mitoxantrone arm (34% *vs.* 22.6%) with twofold more grade ≥3 TEAEs (10.2% *vs.* 5.1%). Anaemia (based on hemoglobin laboratory values) was observed in the vast majority of patients in both the cabazitaxel (97.0%) and the mitoxantrone groups (81.4%) in Study EFC6193. The incidence of Grade ≥ 3 anaemia was higher with cabazitaxel (10.5%) than with mitoxantrone (4.9%).

Nervous system disorders
Nervous system disorders were significantly more common in Cabazitaxel group compared to mitoxantrone arm. Peripheral neuropathies were of higher rate in Cabazitaxel arm (13.5% vs 3.2% mitoxantrone). In the pivotal study, there were 18 patients with HLT paresthesia and dysesthesia, and 50 patients with HLT peripheral neuropathy treated with cabazitaxel presented an event of peripheral neuropathy or paraesthesias and dysaesthesias. A review of these cases shows in general, grades 1 and 2 events without any action taken, except few delayed and reduced doses. Two patients with grade >3 peripheral neuropathy were 74 and 80 year-old.
In phase 1/phase 2 studies, peripheral sensory neuropathy is reported in almost one-third of patients.

Cardiac disorders
All Grade events among cardiac disorders were more common on cabazitaxel of which 6 patients (1.6%) had Grade ≥3 cardiac arrhythmias. The incidence of tachycardia on cabazitaxel was 1.6%, none of which were Grade ≥3. The incidence of atrial fibrillation was 1.1% in the cabazitaxel group. Cardiac failure events were more common on cabazitaxel, the event term being reported for 2 patients (0.5%). One patient in the cabazitaxel group died from cardiac failure. Fatal ventricular fibrillation was reported in 1 patient (0.3%), and cardiac arrest in 2 patients (0.5%). None were considered related by the investigator.

Gastrointestinal disorders
The percentage of gastrointestinal disorders is significantly more important in the cabazitaxel groups when compared to mitoxantrone administration (73.3% *vs.* 48%). All treatment-emergent AEs and grade ≥3 are significantly more common in cabazitaxel arm: in particular, diarrhoea, nausea, vomiting, abdominal pain, dyspepsia, gastrointestinal vascular conditions. Some AE were even more pronounced in phase 1/ phase 2 studies in the group with ≥25 mg/m² cabazitaxel: abdominal pain 32.6%, nausea and vomiting 55.8%, stomatitis 16.3%.

Skin and subcutaneous disorders
Skin and subcutaneous disorders were more observed in cabazitaxel group compared to mitoxantrone group during the pivotal trial (21.8% cabazitaxel group 16.4% mitoxantrone group). Twice as many patients suffered from alopecia in cabazitaxel group compared to mitoxantrone (10.0% cabazitaxel group, 4.9% mitoxantrone group). Alopecia was particularly observed in patients (30.2%) treated with high dose of cabazitaxel (≥25 mg/m²) that include the dose proposed for studied indication.

Renal and urinary disorders
Significantly higher incidence of renal failure and acute renal adverse events is reported in patients treated by Cabazitaxel compared to those treated by mitoxantrone (30.7% Cabazitaxel, 11.3% mitoxantrone), however urinary tract signs and symptoms were the predominant reasons. The trend of high frequency of renal and urinary disorders was also confirmed during phase 1/phase 2 studies.
Hematuria is very common in patients with prostate cancer, yet was more frequent in the cabazitaxel group (62 patients [16.7%] all grades, 7 patients [1.9%] Grade ≥3) than in the mitoxantrone group (14 patients [3.8%] all grades, 2 patients [0.5%] Grade ≥3).

Serious adverse event/deaths/other significant events

Serious adverse events:
In study EFC6193, serious TEAEs were reported in 39.1% of patients in the cabazitaxel group and 20.8% of patients in the mitoxantrone group. The most common Grade ≥3 serious adverse events (SAEs) (≥1%) in the cabazitaxel group were febrile neutropenia (6.7%), neutropenia (4.9%), diarrhea (1.9%), pneumonia (1.3%), and renal failure acute (1.1%). The most common Grade ≥3 SAEs in the mitoxantrone group were disease progression (3.0%) and febrile neutropenia (1.1%). The pattern of SAEs is similar to that of AEs in general, with hematologic and gastrointestinal toxicity among the most prominent. SAEs also included events attributable to the consequences of these, notably infection and renal failure.

Deaths:
In study EFC6193, the percentage of patients who died from TEAEs (other than progressive disease) within 30 days of last infusion was 4.9% in the cabazitaxel group compared with 1.9% in the mitoxantrone group. Of the 18 patients who died in the cabazitaxel group, 7 of these were attributed to neutropenia and its consequences: neutropenic sepsis (2); fungal sepsis; sepsis; septic shock (with associated enterocolitis and renal failure); pancytopenia; and, a case of vomiting and aspiration in the setting of neutropenia. Six (6) of these were considered related to study treatment.

There were 5 deaths due to cardiac events: cardiac arrest (2); cardiac failure; dyspnoea; and, ventricular fibrillation. Three fatal cases of renal failure were reported: renal failure (2); and, renal failure and respiratory failure. One (1) case of electrolyte imbalance (in the setting of diarrhoea after home treatment for constipation) was included among the fatal cases. There were two "other" cases: cerebral haemorrhage (intracranial haemorrhage after a fall); and, a sudden death (at home).

Data from Phase 1/2 studies:
In the Phase 1/Phase 2 studies, the number of TEAEs, serious TEAEs, the number of patients withdrawing from study treatment, and deaths within 30 days of last infusion of study drug were mostly similar to those reported in the Phase 3 study EFC6193. The main haematological AE was neutropenia, occurring in more than 90% of patients with the majority of patients experiencing at least grade 3 neutropenia. Gastrointestinal disorders including diarrhoea, nausea, vomiting and anorexia were also of very frequent rate.
The number of patients who died was similar to those observed in the Phase 3 study EFC6193 (<25 mg/m² cabazitaxel: 80.9%; ≥25 mg/m² cabazitaxel: 60.5%; weekly cabazitaxel: 61.8%). The majority of deaths were due to disease progression. One death in study TED6188 (30 mg/m²) was due to neutropenic (pulmonary) infection; 1 death in study ARD6191 (20 mg/m²) was due to cyanosis and dyspnoea (from multiple causes); and one for unknown reasons (possibly a sudden cardiac death). One (1) patient in study TED6189 who was given cabazitaxel at the highest weekly dose (12 mg/m²) died due to pneumonia that occurred 21 days after the last dose of study drug.
Serious TEAEs were reported in 31.5%, 37.2%, and 45.5% of patients in each of the 3 treatment groups (<25 mg/m² cabazitaxel, ≥25 mg/m² cabazitaxel, and weekly cabazitaxel). The proportion of patients withdrawing from study treatment due to any TEAE (including disease progression reported as a TEAE) was 3.4%, 9.3%, and 16.4% in each of the 3 treatment groups.

Laboratory findings

In the Phase 3 study EFC6193, patients treated with cabazitaxel experienced more myelosuppression resulting in a higher incidence of neutropenia and anaemia. Especially, grade ≥3 neutropenia was high (81.7%) in patients in the cabazitaxel group compared with those in the mitoxantrone group (58.1%). Thrombocytopenia was reported slightly more frequently with the reference product.
Slight differences were observed in liver and renal function chemistry results between cabazitaxel and mitoxantrone treated arms. No hepatobiliary disorders were observed during the studies with cabazitaxel. The incidence of grade ≥3 anaemia, increased AST, ALT, and bilirubin based on laboratory abnormalities were 10.6%, 0.7%, 0.9%, and 0.6%, respectively. Four cases of renal failure have been reported in cabazitaxel group and none in mitoxantrone group.

Safety in special populations

Renal insufficiency:
The safety of Cabazitaxel has not been evaluated in patients with renal disorders. However, cases of renal failure including cases with fatal outcome have been reported.
In the proposed SmPC, it is stated that no dosage adjustment is necessary in patients with mild renal impairment, that patients with moderate and severe renal impairment should be treated with caution and monitored carefully during treatment and that dosage delay or reduction should be considered in the event of adverse drug reactions. The applicant has been requested to further investigate the PK in patients with moderate and severe renal impairment as part of study POP12251 reflected in the RMP (see 2.6)

Hepatic insufficiency:
The safety of cabazitaxel has not been evaluated in patients with severe hepatic dysfunction. Cabazitaxel is therefore contra-indicated in patients with hepatic impairment defined as bilirubin ≥1 x ULN, or AST and/or ALT ≥1,5 x ULN, as listed in section 4.3 of the SmPC.
In order to recommend appropriate dose modifications in patients with hepatic impairment, the applicant is currently conducting a Phase I safety and pharmacokinetic study (POP6792) of cabazitaxel in advanced solid tumour patients with varying degrees of hepatic impairment. The study is designed as an open-label, dose-escalation, multicenter study (see 2.7).

Paediatric population:
The safety of Cabazitaxel therapy has not been established in children aged 0 to 18 years of age and a statement has been included in section 4.2 of the SmPC.

Elderly patients:
No specific dose adjustment for the use of cabazitaxel in elderly patients is recommended.
Among the 371 patients treated with cabazitaxel in the prostate cancer phase 3 study, 240 patients were 65 years or over including 70 patients older than 75 years
The following adverse reactions reported at rates ≥5% higher in patients 65 years of age or greater compared to younger patients: fatigue (40.4% versus 29.8%), neutropenia (24.2% versus 17.6%), asthenia (23.8% versus 14.5%), pyrexia (14.6% versus 7.6%), dizziness (10.0% versus 4.6%), urinary tract infection (9.6% versus 3.1%) and dehydration (6.7% versus 1.5%), respectively.
The incidence of the following grade ≥3 adverse reactions were higher in patients ≥65 years of age compared to younger patients; neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinical neutropenia (23.8% versus 16.8%) and febrile neutropenia (8.3% versus 6.1%).

Fertility, pregnancy and lactation:
There are no adequate and well controlled studies in pregnant women with cabazitaxel.
Studies in animals have shown the reproductive toxicity and that cabazitaxel crosses the placenta barrier. cabazitaxel administered once daily to female rats from gestational days 6 to 17 at a dose of 0.16 mg/kg/day (approximately one-tenth to one-twentieth the area under the concentration curve (AUC) in cancer patients at the recommended human dose) caused embryofetal toxicity, due to maternal toxicity consisting of foetal deaths and decreased mean foetal weight associated with a delay in skeletal ossification. Cabazitaxel did not produce foetal abnormalities in rats and rabbits.
Available pharmacokinetics data in animals have shown excretion of cabazitaxel and its metabolites in milk. A risk to the suckling child cannot be excluded and appropriate recommendations have been included in section 4.6 of the RMP.
Considering the pharmacological activity of taxanes, their genotoxic potential and effect of several compounds of this class on fertility in animal studies, effect on male fertility could not be excluded in human.
Due to potential effects on male gametes and to potential exposure via seminal, and the lack of data from the use of cabazitaxel in pregnant women, it is stated in section 4.6 of the SmPC that men treated with cabazitaxel should use effective contraception during the treatment and continue for up to 6 months after the last dose of cabazitaxel. Also Due to potential exposure via seminal liquid, men treated with cabazitaxel should prevent contact with the ejaculate by another person throughout treatment.

Immunological events

In the pivotal study, immune system disorders (all grades) were observed in 8 patients (2.2%) in the cabazitaxel group and 0.8% of patients in the mitoxantrone group. These were primarily hypersensitivity disorders, which occurred in 5 patients (1.3%), treated with cabazitaxel and no patients treated with mitoxantrone. All hypersensitivity events were Grade 1 or 2. Three of these 5 patients in the Cabazitaxel group had a hypersensitivity reaction that resulted in a dose interruption.
Ten cases of hypersensitivity have been reported in the Phase 1/Phase 2 studies; five were Grade ≥3. Three of these events, one anaphylactic reaction and two hypersensitivity reactions were considered serious.
Allergic conditions and hypersensitivity to cabazitaxel, to other taxanes therapy or any excipients of the formulation including Polysorbate 80 are contra-indicated for the use of this product. In addition, hypersensitivity reactions should be closely monitored.

Safety related to drug-drug interactions and other interactions

At the time of the dossier cut-off date, no specific studies have been carried out to assess the effect of inhibitors or inducers of CYP3A on the pharmacokinetics of Cabazitaxel. The effect of weak CYP3A inducers (*eg.* prednisone or prednisolone) has been evaluated in the population PK analysis. No specific studies have been performed to investigate the impact of Cabazitaxel on CYP3A sensitive substrates.
No formal clinical drug-drug interaction studies have been completed with Cabazitaxel.
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, may result in serious or fatal infections. The concomitant vaccination with yellow fever vaccine was contraindicated and appropriate recommendations regarding vaccination have been included in section 4.5 of the SmPC.

Discontinuation due to adverse events

More patients discontinued the study due to disease progression in the mitoxantrone group compared to cabazitaxel group, 72.2% *vs.* 48.2%. However the number of discontinuations due to TEAES was approximately 2-fold higher in the cabazitaxel-treated group compared to the mitoxantrone-treated group (cabazitaxel: 18.3% versus mitoxantrone: 8.4%). The number of discontinuation was very high in the phase 1 and 2 trials, only 7.9%, 7% and 1.8% patients completed the study. In TCD6945 combination study, not any patient completed the study treatment period.
Nine patients (2.4%) discontinued the cabazitaxel treatment due to Grade ≥3 neutropenia and 3 patients more due to febrile neutropenia in the pivotal study compared to zero patient in mitoxantrone arm.

2.6.1. Discussion on clinical safety

The clinical development programme of cabazitaxel included 591 subjects who received at least one dose of cabazitaxel, regardless of the dosage and treatment duration.
Clinical safety analysis is based on 4 phase 1, two phase 2 and one phase 3 studies. Only one phase 3 pivotal, comparative study with 742 patients involved was conducted in the requested indication in combination with prednisone or prednisolone for treatment of patients with metastatic hormone refractory prostate cancer (HRPC) previously treated with docetaxel-based treatment.

415 patients have been treated with a proposed dose range of 25 mg/m² of cabazitaxel, including 371 patients involved in the phase 3 trial and 44 patients involved in the phase 1 and phase 2 studies. Two studies were carried out in patients with metastatic breast cancer, previously treated by taxane therapy.
Different doses and different regimens have been studied during this development programme. The dose levels of 20 mg/m2 and 25 mg/m2 every 3 weeks were defined as the recommended doses for further clinical development. The higher dose of 25 mg/m² of Cabazitaxel every three weeks was chosen for phase 3 pivotal study although fewer patients were studied with a dose of 25 mg/m² of Cabazitaxel in the phase 1 and 2 trials. Safety profile of this higher dose seems to be less satisfactory.
Concerning the regional distribution, the majority of patients were studied in Europe.

The total number of cycles administered was higher in cabazitaxel group (2251) in comparison to mitoxantrone group (1736). It appears that the major effect of the administration of more cycles among cabazitaxel treated patients is the likelihood of a greater number of TEAEs reported. However controlled for cycles, there were more AEs in the cabazitaxel group.

Overall, treatment-emergent AE were reported in higher incidence in the cabazitaxel group, in particular, grade ≥ 3 TEAE. A risk ratio of ≥2 between the cabazitaxel and mitoxantrone treatment groups, confirming more than twofold risk with the use of cabazitaxel when compared to mitoxantrone, was determined for the following AEs: peripheral neuropathy, febrile neutropenia, dysuria, hematuria, diarrhoea, abdominal pain, dysgeusia, dyspnea, vomiting, anemia, alopecia, neutropenia, dyspepsia, peripheral sensory neuropathy, muscle spasms, urinary tract infection, hypotension, mucosal inflammation, and thrombocytopenia.

The number of patients with any TEAE, serious TEAE, grade ≥3 TEAE, and withdrawals due to any TEAE was significantly higher in cabazitaxel group compared to mitoxantrone group of patients.
The SOCs reporting a statistically significant higher incidence of AEs in the cabazitaxel arm were: Gastrointestinal Disorders, Blood and Lymphatic System Disorders, Infections and Infestations, Nervous System Disorders, also observed with other taxane therapies. In addition, a statistically significant higher rate of AEs was reported in cabazitaxel-treated subjects compared with mitoxantrone treated subjects for General Disorders And Administration Site Conditions, Renal And Urinary Disorders, Respiratory, Thoracic And Mediastinal Disorders, Metabolism And Nutrition Disorders.

Overall, the proportion of patients experiencing at least one SAE in the safety population of the phase 3 study was of higher rate in the cabazitaxel arm compared to mitoxantrone arm. Even two-fold higher number of patients treated by cabazitaxel experienced serious AEs and grade ≥3 SAEs. In the phase 1/phase 2 studies, a rate of serious AEs was similar to that of phase 3 study.

In the pivotal study, grade ≥3 neutropenia was thrice as much with cabazitaxel compared to mitoxantrone treatment. Even if the management of these cases and the use of prophylactic or

therapeutic G-CSF are recommended according to ASCO Guideline, the high rate of neutropenia leading to infections and sepsis remains an issue for the use of cabazitaxel.
A dose modification has been included in section 4.2 of the SmPC in patients presenting grade ≥3 neutropenia longer than one week despite appropriate treatment including G-CSF. A warning was also included in section 4.4 of the SmPC describing the risk of neutropenia and providing guidance on its management. Furthermore, cabazitaxel is contraindicated in patients with neutrophil counts less than 1,500/mm^3.
The incidence of Grade ≥ 3 anaemia was twice as higher in patients treated with cabazitaxel than with mitoxantrone. Appropriate recommendations have been included in section 4.4 of the SmPC for patients with haemoglobin <10g/dL.

Cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel. Patients under treatment with cabazitaxel will be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop. Physicians will be recommended to assess for the presence or worsening of neuropathy before each treatment. The treatment with cabazitaxel should be delayed until improvement of symptoms. The dose should be reduced from 25 mg/m^2 to 20 mg/m^2 for persistent grade ≥2 peripheral neuropathy.
Peripheral neuropathy has been considered as an identified risk in the RMP and information was included in sections 4.2, 4.4 and 4.8 of the SmPC. Peripheral neuropathy should be closely monitored in post-marketing setting.

A higher incidence of cardiac arrhythmia was observed in the cabazitaxel group compared to the control group. The Applicant states that no potential risk factors could be readily identified and that there is a lack of clear evidence to suggest that cabazitaxel contributed to these cardiac events. It is therefore difficult to confirm whether cardiac disorders, in particular arrhythmias, could be identified as a potential or confirmed risk after cabazitaxel administration. The Applicant is evaluating the effect of cabazitaxel on QT/Qc interval in cancer patients in study TES10884, which has been designed to meet the current ICH E14 guidance (see section 2.7).
In light of the unknown aetiology of the increased incidence of cardiac deaths and arrhythmias, the Applicant has included the potential risk for cardiac conduction disorders in the SmPC.

Patients experiencing diarrhoea following administration of cabazitaxel could be treated with commonly used anti-diarrhoeal medicinal products. Appropriate measures should be taken to re-hydrate patients. Diarrhoea can occur more frequently in patients that have received prior abdomino-pelvic radiation. Dehydration is more common in patients aged 65 or older. Appropriate measures should be taken to rehydrate patients and to monitor and correct serum electrolyte levels, particularly potassium. Treatment delay or dose reduction may be necessary for grade ≥3 diarrhoea. If patients experience nausea or vomiting, they may be treated with commonly used anti-emetics.
Recommendations and warnings related to the risk of nausea, vomiting, diarrhoea and dehydration were included in sections 4.2 and 4.4 of the SmPC.

Renal failure was often multi-factorial in origin and a direct causal relationship with cabazitaxel cannot be determined. Haematuria is very common in patients with prostate cancer. Although more frequent in the cabazitaxel group, a possible explanation for the observed haematuria was found in most cases. Haematuria should be closely monitored.

In the pivotal study, the number of deaths during on-treatment and post-treatment phase was higher for comparator notably related to deaths from progressive disease. However, the number of deaths within 30 days of last infusion was of significantly higher incidence after Cabazitaxel therapy compared to mitoxantrone therapy. The difference between two groups reflects the high incidence of haematological toxicity of Cabazitaxel in comparison to mitoxantrone. The analysis of fatal cases from the supportive studies confirms that they are frequently due to disease progression, infections.

Hypersensitivity reactions have been reported in patients treated with cabazitaxel. Allergic conditions and hypersensitivity to cabazitaxel, any other taxane therapy or excipients of the formulation including polysorbate 80 is contra-indicated for the use of this product and hypersensitivity reactions should be closely monitored. Premedication should also be performed to mitigate the risk and severity of hypersensitivity (see section 4.2 of the SmPC).

More patients discontinued the study due to disease progression in the mitoxantrone group compared to cabazitaxel group. However, there is a significant difference in the number of discontinuation due to TEAEs other than disease progression in the cabazitaxel group compared to mitoxantrone arm.

No direct comparison to other taxane therapies has been performed by the applicant. A trend of less peripheral oedema was noted with cabazitaxel. A higher incidence of the hematological toxicity was shown as well as more gastrointestinal disorders. In particular, neutropenia occurred in the vast majority of patients. Diarrhoea, fatigue, nausea, vomiting, asthenia, constipation, haematuria and febrile neutropenia were also reported to be significantly more frequent during cabazitaxel therapy. The rate of alopecia and nail disorders seems to be lower than that expected with taxane therapy; however, no firm conclusion can be given.

As it may cause fatigue and dizziness, cabazitaxel may have a moderate influence on the ability to drive and use machines. Adequate recommendation can be found in section 4.7 of the SmPC.

The anticipated complications of overdose would consist of exacerbations of adverse reactions as bone marrow suppression and gastrointestinal disorders. Adequate recommendation regarding overdose can be found in section 4.9 o the SmPC.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of cabazitaxel is associated with a critical safety deterioration compared to mitoxantrone. The number of patients with any TEAE, serious TEAE, grade ≥3 TEAE, the number of deaths within 30 days of last infusion and withdrawals due to any TEAE was always significantly higher in cabazitaxel group compared to mitoxantrone group of patients. A risk ratio of ≥2 between the cabazitaxel and mitoxantrone treatment groups, confirming more than two fold risk with the use of cabazitaxel when compared to mitoxantrone, was determined for many of AEs.

Haematological toxicity of cabazitaxel is of concern. Twice as much aenemias, thrombocytopenias and neutropenia have been reported during the pivotal study in the cabazitaxel arm compared to mitoxantrone arm. Grade ≥3 neutropenia was even thrice as much with cabazitaxel compared to mitoxantrone treatment with notably more febrile neutropenia in cabazitaxel group. Nine patients (2.4%) discontinued the cabazitaxel treatment due to Grade ≥3 neutropenia and 3 patients more due to febrile neutropenia in the pivotal study compared to zero patient in comparative arm. In addition, infections were more frequent in the cabazitaxel-treated arm compared to mitoxantrone arm. Management of these cases is recommended by monitoring of complete blood counts during treatment and before each cycle. Dose modification is presented, including dose reduction after prolonged neutropenia and febrile neutropenia. G-CSF is recommended therapeutically, as secondary prophylaxis, and as primary prophylaxis in clinical settings of increased risk, such as advanced age, poor performance status, extensive radiation, co-morbidities and previous episodes of febrile neutropenia.

No direct comparison to other taxane therapies has been performed by the applicant. Patients who experienced hypersensitivity reactions with previous taxane treatment should not be treated by cabazitaxel.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The Risk Management Plan submitted by the MAA broadly complies with the recommended structure described in Volume 9A of "The Rules Governing Medicinal Products in the European Union".
The most frequently experienced AEs with Cabazitaxel correspond to those classically observed with taxane therapy. Even though no direct comparison to other taxanes has been performed, a higher incidence of hematological AE is observed as well as gastrointestinal disorders.
The Risk management plan proposed by the MAH is summarised on the table below.

Table 28: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified Risks		
Neutropenia and associated clinical events (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock)	Routine pharmacovigilance	Dose recommendations and modification for neutropenia and associated clinical events are discussed in the proposed SmPC Section 4.2, Posology and method of administration; Section 4.3, Contraindications, Section 4.4, Special warnings and precautions for use, Section 4.8 Undesirable effects
Gastro-intestinal disorders (vomiting and diarrhea) and associated complications (dehydration and electrolytes imbalance)	Routine pharmacovigilance	Dose recommendations and modification for diarrhoea and treatment of diarrhoea and dehydration are discussed in the proposed SmPC Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use, Section 4.8 Undesirable effects
Renal failure	Routine pharmacovigilance	Renal failure is discussed in the proposed SmPC Section 4.4, Special warnings and precautions for use, Section 4.8 Undesirable effects
Peripheral neuropathy	Routine pharmacovigilance Clinical AE data collection from LCM clinical trials and cumulative review of peripheral neuropathy in each PSUR	Dose recommendations and modification for peripheral neuropathyare discussed in the proposed SmPC Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use, Section 4.8 Undesirable effects
Anemia	Routine pharmacovigilance Clinical AE data collection from LCM clinical trials	Anemia is discussed in the proposed SmPC Section 4.4, Special warnings and precautions for use, Section 4.8 Undesirable effects
Important Potential Risks		
Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)	Routine pharmacovigilance Additional clinical AE data collection from ongoing LCM clinical trials and cumulative review of cardiac arrhythmia in each PSUR Study TES10884	The incidence of these events is presented in the proposed SmPC Section 4.4, Special warnings and precautions for use, Section 4.8 Undesirable effects.
Hepatic disorders (based on potential class-effect)	Routine pharmacovigilance	Hepatic disorders are discussed in the proposed SmPC Section 4.2, Posology and method of administration; Section 4.3, Contraindications
Lens toxicity (observed in a non-clinical study in rats)	Routine pharmacovigilance Clinical AE data collection from ongoing LCM Clinical trials	Lens toxicity is presented in the proposed SmPC Section 5.3 Pre-clinical safety data
Effect on male fertility (based on nonclinical studies)	Routine pharmacovigilance	Effect on male fertility is discussed in the proposed SmPC Section 4.6 Fertility, pregnancy and lactation
Use in non-evaluated indications	Routine pharmacovigilance	Use in non-evaluated indications is discussed in the proposed SmPC Section 4.1 Therapeutic indications; Section 4.2 Posology and method of administration
Important missing information		
Drug-drug interaction (concomitant administration with CYP3A substrates or with inducers/ inhibitors of CYP3A)	Routine pharmacovigilance Studies TCD10870 and POP6792	Drug-drug interaction is discussed in the proposed SmPC Section 4.2 Posology and method of administration; Section 4.4, Special warnings and precautions for use; Section 4.5 Interactions with other medicinal products; Section 5.2 Pharmacokinetic properties

Use in patients with hepatic impairment	Routine pharmacovigilance Safety and pharmacokinetic study (POP6792)	Use in patients with hepatic impairment is discussed in the proposed SmPC Section 4.2, Posology and method of administration; Section 4.3, Contraindications
Use in patients with moderate and renal impairment	Routine pharmacovigilance study (POP12251)	Use in patients with moderate and renal impairment is discussed in the proposed SmPC Section 4.2 Posology and method of administration; Section 5.2 Pharmacokinetic properties
Ethnicity other than Caucasian	Routine pharmacovigilance Clinical AE data collection from LCM clinical trials	Ethnicity is presented in the proposed SmPC Section 5.1 Pharmacodynamic properties

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

Jevtana is intended for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen in combination with prednisone or prednisolone. In such a population, the goal of the treatment is to improve the overall survival or at least the quality of life. The present submission is based on one single pivotal study. The primary objective was to determine whether cabazitaxel/Prednisone could improve overall survival when compared to mitoxantrone/prednisone. cabazitaxel/Prednisone was associated with a 2.4 month increase in median overall survival compared to mitoxantrone/prednisone.

- Uncertainty in the knowledge about the beneficial effects.

Secondary endpoints such as PFS, tumour response rate and tumour progression were consistent with the primary endpoint. In secondary analyses, a median PFS difference of 1.4 month in favour of cabazitaxel/prednisone was also observed. cabazitaxel/prednisone was also associated with higher response rate and increased time to PSA progression. However, these parameters have inherent limitations due to, among others, ascertainment bias, inter-observer variability and the fact that no independent review of PFS assessment was carried out.
There is some uncertainty about the efficacy in patients that had received less than 225 mg/m^2 of docetaxel. Previous treatment with <225 mg/m^2 cumulative dose of docetaxel was introduced as an exclusion criterion after protocol amendment. A sub-group of 59 patients received prior cumulative dose of docetaxel <225 mg/m² (29 patients in JEVTANA arm, 30 patients in mitoxantrone arm). There was no significant difference in overall survival in this group of patients (HR (95%CI) 0.96 (0.49-1.86)). This observation may be due to a lower efficacy in this subgroup due to different patient or disease characteristics. The low number of patients in this subgroup analysis may also explain the lack of a clear effect. Thus, although there is insufficient evidence to conclude that the benefits are lacking in this subgroup, this information has been included in the SmPC (see section 5.1) to help make an informed treatment choice.

Risks

- Unfavourable effects

The number of patients with any TEAE, serious TEAE, grade ≥3 TEAE and withdrawals due to any TEAE were significantly higher in the cabazitaxel group compared to mitoxantrone. In study EFC6193, the percentage of patients who died from TEAEs (other than progressive disease) within 30 days of last infusion was 4.9% in the cabazitaxel group compared with 1.9% in the mitoxantrone group. Of the 18 patients who died in the cabazitaxel group, 7 of these were attributed to neutropenia and its consequences. The haematological toxicity was also higher for cabazitaxel/predinsone compared to mitoxantrone/prednisone. In Study EFC6193, the incidence of Grade ≥ 3 neutropenia was higher with cabazitaxel than with mitoxantrone (27.5% *vs.* 8.4%), with notably more febrile neutropenia in cabazitaxel group. In addition, infections were more frequent in the cabazitaxel arm compared to mitoxantrone arm. Even with prophylactic or therapeutic G-CSF, cabazitaxel was associated with a higher rate of neutropenia leading to infections and sepsis.

- Uncertainty in the knowledge about the unfavourable effects

As might be expected in the Phase II study, the side effect profile for the < 25mg/m² dose was generally more favourable when compared to the ≥25mg/m² dose. It is unclear whether the <25mg/m² dose would have similar activity to the ≥25mg/m² dose but with a more acceptable safety profile. The Applicant has submitted the protocol of a randomised, open label study comparing cabazitaxel at 20 mg/m² and at 25 mg/m² in second line mHRPC patients.

No direct comparison to other taxane therapies has been performed by the applicant.

Benefit-risk balance

- Importance of favourable and unfavourable effects

The single most influential factor is considered to be the improvement in median overall survival. The pivotal study submitted met both primary and secondary endpoints with the exception of pain response. More subjects experienced an adverse event, a related adverse event or a treatment related death in the cabazitaxel arm. Neutropenia and in particular febrile neutropenia is an important treatment-related side-effect associated with cabazitaxel/prednisone.

- Benefit-risk balance

The CHMP is of the opinion that there is a clear benefit in terms of overall survival associated with cabazitaxel/prednisone compared to mitoxantrone/prednisone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. In a subgroup of patients that received previously less than 225 mg/m^2 of docetaxel, the benefit in OS is not significant, and the information has been added in section 5.1. Despite the increased toxicity associated with cabazitaxel/prednisone, an advantage in overall survival was observed and the effect in terms of this endpoint was considered to be clinically and statistically significant.

2.8.1. Discussion on the benefit-risk balance

The effect in terms of overall survival is similar to what has been observed with other therapies in late line cancers, where dramatic effects in terms of overall survival are rare due to the advanced stage of the disease. Due to the poor prognosis, high unmet clinical need and lack of alternative therapies, the observed benefits in terms of overall survival are considered clinically important. There are no major remaining uncertainties that have an impact on the benefit-risk balance.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns, no additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Jevtana in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen was favourable and therefore recommended the granting of the marketing authorization.