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Sponsor / Company: Sanofi	**Study Identifiers:** NCT01140607, U1111-1116-5845
Drug substance(s): XRP6258 (cabazitaxel)	**Study code:** POP6792

Title of the study: Phase 1 Safety and Pharmacokinetic Study of XRP6258 (Cabazitaxel) In Advanced Solid Tumor Patients With Varying Degrees of Hepatic Impairment

Cohort 5: drug-drug interaction study with midazolam in advanced solid tumor patients with normal hepatic function

Study center(s): This study was conducted at 7 clinical centers in the United States.

Study period:

Date first patient enrolled: 27/Oct/2010

Date last patient completed: 30/Apr/2011 (last patient completed for Cohort 5)

Phase of development: Phase 1 Safety, Pharmacokinetics and Drug-Drug Interaction

Objectives: To assess the effect of cabazitaxel at recommended dose of 25 mg/m^2 on CYP3A enzyme activity using midazolam as probe in cancer patients with normal hepatic function.

In addition, safety was evaluated.

Methodology: An open-label, multicenter study. Cohort 5 enrolled only patients diagnosed with solid tumors and with normal hepatic function.

Number of patients:	Planned: Approximately 12 patients for Cohort 5
	Randomized: 13
	Treated: 13
Evaluated:	Safety: 13
	Pharmacokinetics: 11

Diagnosis and criteria for inclusion: Patients with a diagnosis of advanced, measurable or non-measurable, non-hematological cancer, who have normal hepatic function. The cancer must have been the one that is either refractory to standard therapy or for which no standard therapy exists.

Study treatments

Investigational medicinal product(s): cabazitaxel (XRP6258) as 60 mg/1.5 mL concentrate and solvent for solution for infusion.

Formulation: concentrate (containing Polysorbate 80 from vegetable origin) and solvent (containing 13% w/w ratio of ethanol in water) for solution for infusion

Route(s) of administration: intravenous (IV)

Dose regimen: 25 mg/m^2 IV infusion over 1 hour on Day 1 of each 3-week cycle

Noninvestigational medicinal product(s): midazolam

Formulation: 1 mg/mL solution for injection (Baxter)

Route(s) of administration: oral, followed by 200 mL of plain water, in fasting conditions

Dose regimen: 2 mg once a day: on Day -1, 24 hours before cabazitaxel infusion; and on Day 1 at the end of cabazitaxel infusion.

Duration of treatment: Midazolam was administered at Cycle 1 only. For cabazitaxel, after Cycle 1, patients had the option to continue receiving cabazitaxel as long as they were benefiting from it and provided there was no unacceptable toxicity, or need to use anticancer treatment other than cabazitaxel.

Duration of observation: The study cut-off date for full data collection was when the last patient completed Cycle 1 and the subsequent 30 day follow-up.

Criteria for evaluation:

Safety: The safety analysis was based on the reported adverse events (AEs) and serious adverse events (SAEs), clinical laboratory data (hematology and blood chemistry), vital sign assessments, and electrocardiogram parameters. After cut-off date (30 April 2011), only reported SAEs were captured.

Pharmacokinetics: The following pharmacokinetic (PK) parameters were calculated from plasma concentrations of midazolam using non-compartmental analysis:

- Primary endpoint:
    - midazolam: Area Under the Time Concentration Curve (AUC), AUC_{last}

- Secondary endpoint:
    - midazolam: Maximal observed concentration (C_{max}), time to reach maximal concentration (t_{max}), and terminal half-life ($t_{1/2z}$)
    - Cabazitaxel: C_{max}, t_{max}, and AUC_{last}

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples for determining midazolam plasma concentrations were collected at the following times on Cycle 1, Day -1 and Day 1: before dosing, then 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours post midazolam administration. The predose sample from Day 1 (taken 55 minutes after the start of infusion of cabazitaxel) was also the 24-hour sample of Day -1.

Blood samples for determining cabazitaxel plasma concentrations were collected at the following times on Cycle 1, Day 1: before the start of infusion, 5 min before the end of infusion and then 5 minutes, 15 minutes, 1, 3, 10, 24, and 168 hours (Day 8) after the end of cabazitaxel infusion.

Midazolam plasma concentrations were determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (DOH0571) with a lower limit of quantification (LLOQ) of 0.1 ng/mL, under the responsibility of Covance, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, UK. All raw data from the bioanalytical study for midazolam were stored at Covance, Alnwick.

Cabazitaxel plasma concentrations were determined using a validated LC-MS/MS method (DOH0958 [PBRL-RD-1190]) with a LLOQ of 1 ng/mL, under the responsibility of PRA International – Early Development Services, Bioanalytical Laboratory, Westerbrink 3 , 9405 BJ Assen, The Netherlands. All raw data from the bioanalytical study for cabazitaxel were stored at PRA International, Assen, The Netherlands.

Statistical methods:

Safety:

Safety evaluations were performed on the all-treated population, defined as all patients exposed to at least part of 1 dose of cabazitaxel. Evaluations of safety were based on the review of individual values and descriptive statistics.

The relationship between safety parameters Grade 3 and 4 (neutropenia, febrile neutropenia, diarrhea and dehydration), lab values (% of decrease in neutrophil counts, liver function test) at cycle 1 and the PK parameters AUC, C_{max} and Clearance (CL) for cabazitaxel were analyzed by fitting a logistics regression model. Odd ratio and its 95% confidence interval (CI) were reported.

Pharmacokinetic:

Pharmacokinetic parameters of midazolam (C_{max}, t_{max}, AUC_{last}, AUC, and $t_{1/2z}$) were summarized by descriptive statistics for midazolam alone (Day -1) and after co-administration midazolam with cabazitaxel (Day 1).

Treatment ratios midazolam + cabazitaxel versus midazolam alone for AUC and AUC_{last} were listed by subject and summarized using the same descriptive statistics as above.

Log transformed AUC and AUC_{last} was evaluated according to a linear mixed effects model:

- Log (parameter) = Subject + Treatment + Error

With a fixed term for treatment and a random term for subject, fitted by estimated generalized least squares (GLS) with restricted maximum likelihood (REML) estimates of random effects, using SAS PROC MIXED.

Estimate and 90% CI for the geometric means ratio of midazolam co-administered with cabazitaxel versus midazolam alone were provided for AUC and AUC_{last}.

For AUC and AUC_{last}, estimates and 90% CIs of ratios midazolam + cabazitaxel versus midazolam alone of geometric means was obtained by computing estimates with 90% CIs for the difference in the means of log-transformed data in the mixed model framework. The antilog of the confidence limits obtained constituted the 90% CI.

A correction for carry-over effect was applied to midazolam PK parameters on Day 1 before statistical analysis.

Cabazitaxel PK parameters were summarized by descriptive statistics (mean, geometric mean, median, standard deviation [SD], standard error [SE], covariance [CV], minimum and maximum).

Summary:

Population characteristics: A total of 13 patients were enrolled in POP6792 Cohort 5 and received at least 1 cycle of cabazitaxel. The majority of patients were Caucasian (10, 76.9%) and male (8, 61.5%). The mean age at study entry was 54.1 (range 45 to 60) years. Nine of 13 (69.2%) patients had an enrollment Eastern Cooperative Oncology Group Performance Status of 1. The most frequent primary tumor was lung (4 patients), followed by colon and pancreas cancer (2 patients each), with a median time from initial diagnosis of 1.31 years. Twelve of 13 (92.3%) patients had metastatic disease at baseline.

Safety results: No patients permanently withdrew from study drug treatment due to AEs. Four patients experienced a serious treatment-emergent adverse event (TEAE) and 2 patients experienced dose-limiting toxicity. There were 4 deaths reported, all due to disease progression and 1 of these deaths was within 30 days of last drug dose.

Based on drug exposure, the AE profile, and laboratory abnormalities, no new safety findings were observed among Cohort 5 patients in this study.

Pharmacokinetic results:

Estimates and 90% CI of midazolam parameters treatment ratio are presented in the table below:

PK parameters	Cohort 5		
	Cabazitaxel dose level (25 mg/m^2)		
	(N=11)		
	Ratio (midazolam with cabazitaxel vs. without cabazitaxel)	90% CI	Imprecision (%)
AUC* (ng.h/mL)	0.97	(0.76,1.23)	21.25
AUClast (ng.h/mL)	1.04	(0.81,1.34)	22.07

* One patient (840010501) with AUC extrapolation >30% is excluded from the treatment ratio calculation on AUC.

Note: Adjusted AUC and Adjusted AUC$_{last}$ in Day 1 (Midazolam with Cabazitaxel) are used for the treatment ratio calculation on AUC and AUC$_{last}$ respectively.

The ratio of AUC of midazolam administered alone or with cabazitaxel (25 mg/m^2 administered as a single 1-hour infusion) was 0.97 with 90% CI (0.76 to 1.23). The ratio of AUC$_{last}$ of midazolam was 1.04, with 90% CI (0.81 to 1.34).

Cabazitaxel had no effect on the PK of midazolam and thus, is not considered a CYP3A4 inhibitor.

Issue date: 16-Jul-2015

Sponsor / Company: Sanofi	Study Identifiers: NCT01140607, U1111-1116-5845
Drug substance(s): XRP6258 (cabazitaxel)	Study code: POP6792

Title of the study: Phase 1 Safety and Pharmacokinetic Study of XRP6258 (Cabazitaxel) In Advanced Solid Tumor Patients With Varying Degrees of Hepatic Impairment
Cohorts 1 to 4: Patients with Varying Degrees of Hepatic Impairment

Study center(s): This study was conducted at 9 clinical sites in the United States.

Study period:
Date first patient enrolled: 18/May/2010
Study cut-off date: 16/Jun/2014 (last patient completed Cycle 1 treatment and the subsequent 30-day follow-up)
Last patient last visit: 22/Jul/2014 (last patient completed treatment)

Phase of development: Phase 1

Objectives: The objectives of Cohorts 1 to 4 of this study were:
- To determine the maximum tolerated dose (MTD) and safety of cabazitaxel administered to advanced solid tumor patients with varying degrees of hepatic impairment.   - To determine the pharmacokinetics (PK) of cabazitaxel in patients with varying degrees of hepatic impairment.   - To correlate PK variables with pharmacodynamic (PD) safety parameters in order to guide prescribers with regard to dosing in this patient population.

Methodology: This was an open-label, dose-escalation, multicenter study of the safety and pharmacokinetics of cabazitaxel in non-hematological cancer patients with varying degrees of hepatic impairment. The dose escalation for patients with hepatic impairment (Cohorts 2, 3, and 4) was based on the observation of dose-limiting toxicities (DLTs) in Cycle 1.

Number of patients:	Planned: Between 39 and 75
	Randomized: 43
	Treated: 43
Evaluated:	
	Safety: 43
	DLT-evaluable: 38
	Pharmacokinetics: 38

Diagnosis and criteria for inclusion: Patients with a diagnosis of advanced, measurable or non-measurable, non-hematological cancer, who had varying degrees of hepatic function (normal, mild impairment, moderate impairment, or severe impairment). The cancer must have been one that was either refractory to standard therapy or for which no standard therapy exists.

Study treatments	
	Investigational medicinal product(s): Cabazitaxel (XRP6258) as 60 mg/1.5 mL concentrate/solvent for solution for infusion.
	Formulation: Concentrate (containing polysorbate 80 from vegetable origin) and solvent (containing 13% w/w ratio of ethanol in water) for solution for infusion.
	Route(s) of administration: Intravenous (IV) infusion over 1 hour
	Dose regimen: Different starting doses were used for each cohort, with dose escalation for patients with hepatic impairment (Cohorts 2 to 4): 25 mg/m^2 for Cohort 1, 20 mg/m^2 for Cohort 2, and 10 mg/m^2 for both Cohort 3 and Cohort 4. Cabazitaxel was administered on Day 1 of each 3-week cycle.

Duration of treatment: Patients were to continue receiving cabazitaxel treatment until unacceptable toxicities, or disease progression, or withdrawal of their consent, or Investigator's decision to discontinue cabazitaxel treatment, or study cut-off, whichever came first. After the cut-off date, patients who were benefiting from cabazitaxel treatment could continue receiving cabazitaxel treatment.

Duration of observation: The study cut-off date for full data collection was when the last patient completed Cycle 1 and the subsequent 30 day follow-up.

Criteria for evaluation:

Safety: The safety analysis was based on the reported DLTs, adverse events (AEs) and serious adverse events (SAEs), clinical laboratory data (hematology and blood chemistry), and vital sign assessments. The DLTs were defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 grading scale.

To be defined as a DLT, the clinical AE or laboratory abnormality must have been cabazitaxel related, as assessed by the Investigator and agreed upon by the Study Committee.

Liver DLTs in patients with hepatic dysfunction (Cohorts 2, 3, and 4) were defined as an increase in total and direct bilirubin and/or transaminase levels to 3 times the baseline value. In addition, a treatment delay due to cabazitaxel related toxicity of more than 2 weeks between cycles was considered a DLT. All other DLTs were defined according to the NCI CTCAE v.4.0 grading scale as follows:

- Non-hematological toxicity Grade 3 or 4 except:
    - Grade 3 fever without documented infection
    - Grade 3 nausea and vomiting in the absence of effective maximal anti-emetic therapy
    - Grade 3 mucositis/stomatitis in the absence of effective symptomatic treatment
    - Grade 3 fatigue
    - Grade 3 anorexia
    - Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) or bilirubin elevation that returns to baseline prior to next treatment cycle (Cohort 1 only)
    - Grade 3 hypersensitivity reaction in the absence of required pre-medication
    - Peripheral neuropathy Grade 3 that returns to Grade 2 or less at the initiation of the next treatment cycle
- Hematological toxicity, defined as:
    - Febrile neutropenia: fever (of unknown origin without clinically or microbiologically documented infection) ≥38.5°C with neutropenia Grade 3 or 4
    - Neutropenia Grade 4 lasting >7 days
    - Thrombocytopenia Grade 4

Pharmacokinetics: Non Compartmental Analysis (NCA) was used to calculate: maximum observed concentration (C_{max}), concentration observed at the end of infusion (C_{eoi}), first time to reach C_{max} (t_{max}), time post-dose corresponding to the last concentration above the limit of quantification (t_{last}), area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last} (AUC_{last}), area under the concentration versus time curve calculated using the trapezoidal method from time 0 to 24 hours (AUC_{0-24}), area under the concentration versus time curve calculated using the trapezoidal method from time 0 to 72 hours (AUC_{0-72}), terminal half-life ($t_{1/2z}$), area under the concentration versus time curve extrapolated to infinity (AUC), total body clearance (CL), and volume of distribution at steady state (V_{ss}).

The AUC and subsequent parameters CL and V_{ss} were reported if $t_{1/2z}$ was calculable and if extrapolated area was not higher than 40%.

The CL and V_{ss} were normalized to body surface area (BSA; CL/BSA and V_{ss}/BSA, respectively).

Pharmacokinetic sampling times and bioanalytical methods: Blood samples for determining cabazitaxel plasma concentrations were collected from all patients at the following times on Cycle 1, Day 1: immediately prior to the start of infusion; 5 minutes before the end of infusion; and then 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 5 hours, 7 hours, 10 hours, after the end of infusion; then 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4), 96 hours (Day 5), 168 hours (Day 8), and 216 hours (Day 10) after the beginning of cabazitaxel infusion.

In addition, blood samples were collected from all patients for the determination of the free fraction (protein binding) of cabazitaxel immediately before the start of infusion, 5 minutes before the end of infusion, and then 3 hours after the end of infusion, and 24 hours after the start of infusion.

Cabazitaxel (total) plasma concentrations were determined using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (DOH0958 [PBRL-RD-1190]) with a lower limit of quantification (LLOQ) of 1.00 ng/mL, under the responsibility of PRA International – Early Development Services, Bioanalytical Laboratory, Assen, The Netherlands.

The free fraction of cabazitaxel was determined by equilibrium dialysis, and quantification of free cabazitaxel in buffer after dialysis was determined by LC-MS/MS (method DOH1170, Covance), with a LLOQ of 0.1 ng/mL, under the responsibility of Covance Laboratories Limited, Alnwick, United Kingdom. The plasma dialysates were analyzed as described above for cabazitaxel plasma concentrations in PRA International, Assen, The Netherlands.

Statistical methods: The primary analysis was defined as the frequency of DLTs by planned dose level.

Secondary analyses:

Plasma concentrations and PK parameters of cabazitaxel were summarized by arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV %), median, minimum and maximum.

For PK statistical analysis, log-transformed parameters were calculated.

The effect of the degree of hepatic impairment on cabazitaxel PK parameters was evaluated according to a linear mixed effects model with degree of hepatic impairment as fixed effect using SAS PROC MIXED:

Log (parameter) = Cohort + Error

Estimate and 90% confidence interval (CI) for the geometric mean ratio of each Cohort versus Cohort 1 (patients with normal hepatic function) were provided for CL (and CL/BSA), C_{max}/Dose, AUC/Dose, AUC_{last}/Dose, AUC_{0-24}/Dose and AUC_{0-72}/Dose (normalization to the actual cabazitaxel dose [mg/m^2] for exposure parameters). This analysis was performed on the PK population with exclusions.

Additional analyses:

Due to apparent atypical PK behavior of Cohort 1 (the CL/BSA estimate [13.4 L/h/m2; 90% CI: 8.6-20.8] was in the very low range of the typical CL/BSA determined by the population PK analysis POH0124 [26.4 L/h/m2, CV=38.8%, n=170]), the following additional analyses were performed:

- The effect of the degree of hepatic impairment on cabazitaxel PK parameters was evaluated using the linear mixed effect model versus Cohort 2 (patients with mild hepatic impairment) in addition to the comparison versus Cohort 1 (patients with normal hepatic function). Furthermore, a sensitivity analysis on the effect of hepatic impairment was performed on the PK population with exclusions to assess the impact of patients presenting an erratic PK profile: 1 patient from Cohort 2: 25 mg/m², 1 patient from Cohort 2:20 mg/m², and 1 patient from Cohort 1.

- A comparison of AUC_{0-24} in Cohort 1 (normal) and Cohort 2 (mild) versus the previously reported Cohort 5 (patients with normal hepatic function who received cabazitaxel in coadministration with midazolam, otherwise reported in a separate clinical study report) was performed by linear mixed effect model, in order to establish a bridge between patients with mild hepatic impairment and patients with normal hepatic function within the POP6792 study.

The effect of the degree of hepatic impairment on cabazitaxel PK parameters was assessed assuming no dose effect within each cohort. A lack of dose effect on PK parameters (CL, CL/BSA, AUC_{0-24}/Dose and AUC_{last}/Dose) in the population with hepatic impairment could not be demonstrated using a linear mixed effect model with cohort as fixed effect and dose as covariate.

In addition, the effect of the degree of hepatic impairment compared to Cohort 1 (25 mg/m²) and to Cohort 2 (at the same dose of 25 mg/m²) was also evaluated at each dose level within each cohort, using a mixed model with dose level within cohort as a fixed effect. This assessment was performed for CL, CL/BSA, AUC/Dose, AUC_{0-24}/Dose, AUC_{0-72}/Dose and AUC_{last}/Dose.

The effect of hepatic impairment on free fraction of cabazitaxel (fu) was assessed using a linear mixed effect model with cohort and dose level as fixed effect and time and BSA as continuous variable and patient as random effect.

Summary:

Population characteristics: A total of 43 patients with advanced solid tumors were enrolled and treated: 6 patients in Cohort 1, 18 patients in Cohort 2, 12 patients in Cohort 3, and 7 patients in Cohort 4. All patients had discontinued study treatment at the cut-off date, with the exception of 1 patient in Cohort 2: 20 mg/m², who was on Cycle 31 at the time of cut-off. The most frequent reason for study treatment discontinuation was disease progression, reported in 28 of 43 patients (65.1%). There were also 9 patients that discontinued study treatment because of AEs, and 5 patients that discontinued for reason "other" (3 discontinuations were due to patient's withdrawal of consent, 1 was due to patient's request, and 1 was due to Investigator's decision).

Safety results: The MTD in Cohort 2 (mild hepatic impairment) was established at 20 mg/m², after 3 of the 5 DLT-evaluable patients treated at 25 mg/m² experienced a DLT (60.0%) during Cycle 1. Overall, 3 of 11 DLT-evaluable patients (27.3%) at the MTD experienced a DLT during Cycle 1.

The MTD in Cohort 3 (moderate hepatic impairment) was established at 15 mg/m², after the first 2 patients treated at 20 mg/m² experienced a DLT during Cycle 1. Overall, 1 of the 6 DLT-evaluable patients (16.7%) at the MTD experienced a DLT during Cycle 1.

The MTD in Cohort 4 (severe hepatic impairment) was not established. The first patient treated at 20 mg/m² died 12 days after the first study drug dose of septic shock, tumor lysis syndrome, acute respiratory failure, acute renal failure, and disease progression. Sanofi decided to close enrollment in this cohort, with the agreement of the Food and Drug Administration (FDA). None of the patients treated at a lower dose level (10 or 15 mg/m²) experienced a DLT during Cycle 1.

There were no liver DLTs observed, with reported DLTs being hematological in 8 patients, and non-hematological in 8 patients (with 3 patients experiencing both hematological and non-hematological DLTs).

The majority of deaths reported (21 of 23) were considered due to disease progression. The other 2 deaths were assessed as possibly related to cabazitaxel: Candida sepsis at 20 mg/m^2 in Cohort 2 (MTD); and septic shock and tumor lysis syndrome, in the context of acute respiratory failure, acute renal failure, and disease progression at 20 mg/m^2 in Cohort 4.

The most commonly observed treatment-emergent AEs (TEAEs) in the study were general disorders of fatigue (53.5% of all patients) and peripheral edema (25.6%); hematological events of neutropenia (41.9%) and anemia (37.2%); and gastrointestinal events of diarrhea (39.5%), nausea (39.5%), vomiting (34.9%), and abdominal pain (27.9%). The most commonly reported TEAEs overall were observed across all cohorts studied.

The analysis of related AEs, AEs of Grade ≥3, SAEs, and AEs leading to discontinuation did not reveal any trends related to hepatic impairment.

Pharmacokinetic results: The PK population is composed of all 6 patients in Cohort 1, 15 of 18 patients in Cohort 2 (9 at 20 mg/m^2 and 6 at 25 mg/m^2), 11 of 12 patients in Cohort 3 (2 at 10 mg/m^2, 7 at 15 mg/m^2, and 2 at 20 mg/m^2) and 6 of 7 patients in Cohort 4 (2 at 10 mg/m^2, 3 at 15 mg/m^2, and 1 at 20 mg/m^2).The patients from Cohort 3 at10 mg/m^2 were excluded from the statistical analysis.

The CL/BSA estimate in Cohort 1 (13.4 L/h/m^2; 90% CI: 8.6-20.8) was in the very low range of the typical cabazitaxel clearance determined by population PK analysis (POH0124) (26.4 L/h/m^2, CV=38.8%, n=170). Because of these low values of CL/BSA in Cohort 1, this made an assessment of the effect of hepatic impairment on cabazitaxel PK by comparison with Cohort 1 impractical.

The CL/BSA estimate in Cohort 2 (23.5 L/h/m^2; 90% CI: 17.6-31.4) was in the range of those typically observed in previous studies (POH0124) suggesting that mild hepatic impairment has no effect on cabazitaxel PK parameters. While a comparison of Cohort 2 to Cohort 1 showed a 75% increase of CL/BSA in Cohort 2 (ratio=1.75; 90% CI: 1.04-2.96), it is likely this is due to the lower than normal CL/BSA values for Cohort 1.

A comparison of Cohorts 3 and 4 to Cohort 2 showed a 19% increase of CL/BSA in Cohort 3 (ratio=1.19; 90% CI: 0.74-1.91), while a 23% decrease of CL/BSA (ratio=0.77; 90% CI: 0.39-1.53) was observed in Cohort 4. The opposite trend was observed for AUC parameters; the highest magnitude effect was observed in AUC$_{last}$/Dose, which showed a 14% decrease in Cohort 3 (ratio=0.86; 90% CI: 0.50-1.46) and a 17% increase in Cohort 4 (ratio=1.17; 90% CI: 0.63-2.14).

A sensitivity analysis performed after exclusion of patients with an erratic cabazitaxel PK profiles showed consistent findings, with a 6% decrease of CL/BSA in the moderately impaired patients (ratio=0.94; 90% CI: 0.64-1.38) and a 39% decrease of CL/BSA in the severely impaired patients (ratio=0.61; 90% CI: 0.36-1.05).

A lack of dose effect on CL parameters within the hepatic impaired patients could not be statistically demonstrated and, therefore, the effect of hepatic impairment on cabazitaxel CL parameters was investigated assuming no effect of dose.

No effect of hepatic impairment could be demonstrated on the free fraction of cabazitaxel, which was approximately 6.1%. Free drug PK would therefore lead to the same conclusion as for total drug.

There is no evidence that the lower MTD in patients with mild or moderate hepatic impairment compared to the approved cabazitaxel dose in prostate cancer indication (25 mg/m^2) is due to higher cabazitaxel exposure.

In an analysis of the relationship between safety and PK parameters, there was no significant correlation found between Grade 3, 4 TEAEs and PK parameters, or between Grade 3, 4 laboratory abnormalities during Cycle 1 and PK parameters. The study cohort (hepatic function) was not selected as a statistically significant covariate in any of the logistic regression models under the situation of the PK parameter kept in the model.

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