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Sponsor / Company: Sanofi Drug substance(s): XRP6258 (Cabazitaxel)	Study Identifiers: NCT01527929, UTN U1111-1121-4512, EudraCT 2011-001517-14 Study code: POP12251
Title of the study: An open-label pharmacokinetic and safety study of cabazitaxel in patients with solid tumors with moderately and severely impaired and with normal renal function	
Study center(s): 7 sites in Belgium, Italy, the Netherlands, Spain, and the United Kingdom	
Study period: Date first patient enrolled: 12/Apr/2012 Date last patient completed: 11/Nov/2013	
Phase of development: Phase 1 (population study)	
Objectives: Primary Objective: To study the effect of moderate and severe renal impairment on the pharmacokinetics (PK) of cabazitaxel (CBZ). Secondary Objective: To assess the safety of CBZ in patients with moderate and severe renal impairment.	
Methodology: This was an open-label multicenter study in patients with advanced solid tumors with various degrees of renal impairment to determine PK and to assess tolerability of CBZ administered intravenously in 3 weekly cycles. Eight patients were to be enrolled to each of the following 3 cohorts: • Cohort A: Normal renal function with creatinine clearance (CrCl) >80 mL/min/1.73m^2 • Cohort B: Moderate renal dysfunction with 30 mL/min/1.73m^2 ≤CrCl <50 mL/min/1.73m^2 • Cohort C: Severe renal dysfunction with CrCl <30 mL/min/1.73m^2	
Number of patients: Planned: Up to 24 patients Enrolled: 26 patients Treated: 25 patients Evaluated: Efficacy: 25 Patients Safety: 25 patients Pharmacokinetics: 24 patients	
Diagnosis and criteria for inclusion: Patients with a diagnosis of advanced non-hematological cancer who had moderate and severe degrees of renal impairment, and patients with normal renal function calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).	

Study treatments

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

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

Route(s) of administration: Intravenous (IV)

Dose regimen: Cabazitaxel was administered on Day 1 of each 3-week cycle. Patients received CBZ administered by IV infusion over 1 hour at the dose specified for each cohort.

The starting dose of CBZ was to be 25 mg/m^2 (cohort A and B); for cohort C, the starting dose was 20 mg/m^2 at Cycle 1, then 25 mg/m^2 every 3 weeks if no protocol specific dose limiting toxicities (DLTs) were observed.

Duration of treatment: Patients were to continue on treatment until they experienced unacceptable toxicities/adverse events (AEs), disease progression, withdrew their consent or the investigator decided to withdraw the patient, or study cutoff date, whichever occurred first.

Duration of observation: There was to be a 30-day follow-up visit after the last dose of study medication. Any serious AEs still ongoing at the end of study treatment and any AEs considered related to study treatment still ongoing or occurring after the end of study treatment were to be followed until resolution/stabilization.

Criteria for evaluation:

Pharmacokinetics: Primary: Area under the plasma concentration versus time curve (AUC), AUC using the trapezoidal method from time 0 to 72 hours (AUC_{0-72}), AUC using the trapezoidal method from time 0 to the last measurable concentration (AUC_{last}), and cabazitaxel clearance (CL)

Secondary: Terminal half-life ($t_{1/2z}$ for non-compartmental analysis [NCA] or $t_{1/2\lambda 3}$ for 3-compartmental individual modeling), maximum plasma concentration observed (C_{max}), volume of distribution at steady state (V_{ss})

Standard NCA was used to determine AUC_{0-72}, AUC_{last}, C_{max}, and $t_{1/2z}$. 3-compartmental individual modeling was used to determine AUC, CL, V_{ss}, and $t_{1/2\lambda 3}$.

V_{ss} and CL normalized by body surface area (BSA) were also calculated.

Safety: Adverse events (AEs) reported by the patient or noted by the Investigator. Standard hematology and blood chemistry laboratory assessments.

Efficacy: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by the Investigator.

Pharmacokinetic sampling times and bioanalytical methods: Blood samples (2 mL each) for PK analyses were to be collected from all patients at Cycle 1 and at Cycle 2, in case of dose escalation (cohort C), before 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, and approximately 8 hours post-infusion, and on Day 2 (approximately 24 hours), Day 3 (approximately 48 hours), Day 4 (approximately 72 hours), Day 6 (approximately 120 hours), Day 8 (approximately 168 hours), and Day 10 (approximately 240 hours) after the end of infusion.

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

Total CBZ concentrations in plasma were analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS) with a lower limit of quantification (LLOQ) of 1 ng/mL. Unbound CBZ concentrations in dialysate were analyzed using LC-MS/MS with a LLOQ of 0.025 ng/mL.

Statistical methods: Plasma concentration and PK parameters of CBZ were summarized using descriptive statistics for each population group by arithmetic and geometric means, standard deviation, standard error, coefficient of variation (CV%), median, minimum, maximum, and number of available observations.

For PK statistical analysis, the log-transformed AUCs (AUC_{last}, AUC_{0-72}, AUC) and C_{max} normalized with the actual dose (mg/m^2), CL and V_{ss} (with and without normalization by BSA), $t_{1/2z}$ (NCA) and $t_{1/2\lambda 3}$ (individual modeling) were calculated.

The effect of population group on a single dose of CBZ PK parameters was analyzed using a linear fixed effects model. Regression models were fit for the logarithm (log) of each PK parameter using as the independent variable the log of the calculated creatinine clearance (CrCl by CKD-EPI). Log of BSA was used as a covariate except in models using BSA normalized parameters. Estimate and 90% confidence interval (CI) for the geometric means ratio of each population group versus the normal population group were provided for all PK parameters.

Summary:

Population characteristics: A total of 32 patients were screened for potential registration. Out of the 27 registered patients, 25 patients were administered cabazitaxel in 5 participating countries at 8 investigational centers (1 withdrawn): (8 patients in cohort A, 8 patients in cohort B, and 9 patients in cohort C). Patients numbers treated per country (and per center) are distributed as follows: Italy: 5; Netherlands: 4 (3;1); Belgium: 8 (2;6); Spain: 6; UK: 2 (2;0).

All of the 25 treated patients permanently discontinued treatment. The primary reason for discontinuation was disease progression in 15 patients (60%). Three patients (12%) discontinued due to AE and 2 patients (8%) discontinued following personal request. Five patients (20%) discontinued for other reasons that were mainly based on Investigator's decision (4 of 5), with 1 discontinuation of a cohort C patient being due to renal function deterioration after 20 cycles on an already very low CrCl at study entry (<10mL/min).

Twenty-four patients were eligible for PK analysis by completing the required number of cycles and sample collection (at least 1 cycle for cohort A/normal renal function and cohort B/moderate renal impairment, at least 2 cycles for cohort C/severe renal impairment).

All of the 25 treated patients were Caucasian, 11 (44%) were male and 14 (56%) were female with a balanced distribution within cohorts of either gender. Median age was 58.5 (range 38-72), 65 (42-77) and 66 (44-77) in cohorts A, B, and C, respectively. Patients above 74 years old were 1 (12.5%) and 3 (33.3%) in cohorts B and C, respectively, while 6 (75%), 4 (50%) and 4 (44.4%) of the patients were below 65 years old in cohorts A, B, and C, respectively. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranged from 0 to 2 and were mainly PS 0 (32%) or 1 (64%) for the treated patients.

The most frequent primary tumor site was colon/rectum in 5 patients (20%). In the remaining patients, the primary tumor site was widely distributed across most body organs including cervix in 3 (12%), esophagus in 2 (8%), prostate in 2 (8%), and breast in 2 patients (8%).

Tumor histology was mainly adenocarcinoma in 14 patients (56%), carcinoma in 6 patients (24%), and sarcoma in 2 patients (8%).

The median time from initial diagnosis to first dose was 52 months (range 7-113), 37 months (9-461) and 44 months (16-155) for cohorts A, B, and C, respectively. The majority of patients presented with metastatic disease at study entry (96%).

Of the 25 treated patients, most of them had 3 or more regimens of prior anticancer therapy (60.0%), and a total of 12 patients (48%) had received prior radiation therapy.

Safety results: A total of 140 cycles were administered to 25 patients. The median number of cycles for cabazitaxel was 5 (2-13), 3 (1-15), and 5 (1-20) for patients enrolled in cohorts A, B, and C, respectively. The median relative dose intensity was 91.56% (79.2-99.8), 99.74% (70.2-101.1) and 98.97% (88.8-99.9) for patients enrolled in cohorts A, B, and C, respectively.

All of the 25 patients administered cabazitaxel experienced treatment-emergent AEs (TEAEs) (all grades). Among them, 23 patients (92%) had drug-related TEAEs, 12 patients (48%) had Grade ≥3 TEAEs, 8 patients (32%) had drug-related serious TEAEs, and 3 patients (12%) were discontinued due to TEAEs. No patients experienced TEAEs (regardless of causality to study treatment) leading to death.

The most frequent hematological TEAE Grade ≥3 was febrile neutropenia, experienced by 6 patients (24%) overall, with the distribution of 1 (12.5%), 3 (37.5%), and 2 patients (22.2%) from cohorts A, B, and C, respectively. The most frequent hematological TEAEs by preferred term (PT) (all grades) were febrile neutropenia (24%) and neutropenia (20%).

The most frequent non-hematological TEAE Grade ≥3 was diarrhea, experienced by 4 patients (16%) overall from cohorts B and C only, with the distribution of 2 (25%) and 2 patients (22.2%) from cohorts B and C, respectively. The most frequent non-hematological TEAEs by PT (all grades) were nausea (52%), diarrhea (52%), vomiting (44%), asthenia (40%), and decreased appetite (32%).

The most frequent non-hematological TEAEs by primary system organ class (SOC) were gastrointestinal disorders. They were experienced by 8 (100%), 8 (100%), and 7 patients (77.8%) from cohorts A, B, and C, respectively. Among these, the most frequent TEAEs by PT were nausea (all grades) experienced by 4 (50%), 5 (62.5%), and 4 patients (44.4%), and diarrhea in 5 (62.5%), 4 (50%), and 4 patients (44.4%) from cohorts A, B, and C, respectively.

The second most frequent non-hematological TEAEs by primary SOC were general disorders and administration site conditions. They were experienced by 5 (62.5%), 7 (87.5%), and 6 patients (66.7%) from cohorts A, B, and C, respectively. Among these, the most frequent TEAE by PT was asthenia (all grades) experienced by 3 (37.5%), 4 (50%), and 3 patients (33%) from cohorts A, B, and C, respectively.

Infections and infestations TEAEs (all grades) by primary SOC were experienced by 4 (50%), 5 (62.5%), and 4 patients (44.4%) from cohorts A, B, and C, respectively. Within the infections and infestations SOC, there were a variety of PTs reported, with no PT reported in more than a total of 3 patients. Among PTs with Grade ≥3, 1 cohort C patient experienced serious urinary tract infection and serious pyelonephritis (both considered as not treatment-related by the principal investigator) and 1 cohort A patient experienced serious soft tissue infection. Both of these events resolved by the final visit.

In the injury poisoning and procedural complications primary SOC, a dose reconstitution preparation error occurred (PT "incorrect dose administered") in 1 patient in cohort C, which led to a dose 24% higher than the intended dose (24.8 mg/m^2 instead of 20 mg/m^2). Following administration, the patient experienced fatigue, mucositis, muscle pain, and Grade 3 diarrhea, possibly exacerbated by the medication error, as assessed by the principal investigator. The patient requested to withdraw from the study for tolerability reasons. Fatigue was considered stabilized and all remaining TEAEs were recovered within 1 month after last treatment administration.

Blood and lymphatic system disorders was the most frequently reported SOC for serious TEAEs and were experienced by 1 (12.5%), 3 (37.5%), and 1 patient (11.1%) from cohorts A, B, and C, respectively. The corresponding events (PTs) were all reported as febrile neutropenia and were considered as treatment-related by the Investigator.

Serious TEAEs from the gastrointestinal disorders SOC were experienced by 1 (12.5%), 1 (12.5%), and 2 patients (22.2%) from cohorts A, B, and C, respectively. Most of these serious TEAEs were reported as diarrhea for 1 patient (12.5%) and 1 patient (11.1%) from cohorts B and C, respectively, and were considered as treatment-related by the Investigator.

Serious TEAEs from the infections and infestations primary SOC were experienced by 1 (12.5%), 1 (12.5%), and 2 patients (22.2%) from cohorts A, B, and C, respectively. Most of these serious TEAEs were considered as not treatment related by the Investigator with the exception of an event of soft tissue infection, as mentioned above, that was associated with a low neutrophil count.

With respect to hematology abnormalities, the majority of patients had neutropenia, leukopenia, and lymphopenia, with no specific pattern across cohorts, as well as anemia, which was also frequently reported at baseline. Biochemistry abnormalities, with the exception of anticipated findings directly related to renal function status, were reported in a small number of patients, with no specific pattern of abnormality detected.

Overall, the observed safety profile in the POP12251 study was consistent with the known safety profile of cabazitaxel. No new safety issues were identified.

Pharmacokinetic results: Pharmacokinetic evaluation was performed in 24 patients of the 25 treated (eg, 8 patients per cohort; each of the 8 patients from cohorts A and B were treated with 25 mg/m^2 cabazitaxel at Cycle 1; 8 patients from cohort C were treated with 20 mg/m^2 cabazitaxel at Cycle 1, and 4 patients from cohort C were treated with 25 mg/m^2 cabazitaxel at following cycles [3 patients at Cycle 2 and 1 patient at Cycle 3]). For ease of analysis, the patient assessed for PK at Cycle 3 was included in the Cycle 2 group.

Mean ± SD (Geometric Mean) [CV%]	**Plasma Cabazitaxel**				
	A-normal	**B-moderate**	**C-severe**	**C- severe**	**C-Severe**
	25 mg/m^2	**25 mg/m^2**	**20 mg/m^2**	**25 mg/m^2**	**20 and 25 mg/m^2**
N	8	8	4[b]	4[c]	8
	NCA analysis				
C_{max}	161 ± 57.0	241 ± 207[a]	135 ± 45.7	244 ± 150	
(ng/ml)	(152) [35]	(193) [86]	(130) [34]	(215) [62]	
AUC_{last}	632 ± 376	548 ± 155[a]	516 ± 204	648 ± 265	
(ng•h/ml)	(566) [60]	(532) [28]	(480) [40]	(602) [41]	
AUC_{0-72}	458 ± 342	373 ± 98.8[a]	368 ± 97.2	417 ± 75.6	
(ng•h/ml)	(395) [75]	(361) [26]	(357) [26]	(411) [18]	
$t_{1/2z}$	104 ± 15.0	113 ± 22.6[a]	93.0 ± 30.3	135 ± 73.1	
(h)	(103) [14]	(111) [20]	(88.1) [33]	(115) [54]	
	Compartmental analysis				
AUC	787 ± 177	1070 ± 733	928 ± 475	857 ± 263	
(ng•h/ml)	(766) [23]	(938) [68]	(829) [51]	(823) [31]	
CL	58.9 ± 14.7	54.1 ± 21.9	51.8 ± 34.4	63.0 ± 30.5	
(L/h)	(57.5) [25]	(49.1) [41]	(44.8) [66]	(58.1) [48]	
V_{ss}	7730 ± 3280	6730 ± 2970	5810 ± 1360	6470 ± 3790	
(L)	(7160) [42]	(6170) [44]	(5690) [23]	(5680) [59]	
CL/BSA	33.5 ± 9.76	28.9 ± 10.7	27.5 ± 17.1	31.7 ± 11.4	29.6 ± 13.6
(L/h/(m^2))	(32.5) [29]	(26.5) [37]	(24.1) [62]	(30.3) [36]	(27.0) [46]
Vss/BSA	4230 ± 1360	3580 ± 1480	3130 ± 730	3380 ± 1920	3250 ± 1350
(L/(m^2))	(4040) [32]	(3320) [41]	(3060) [23]	(2970) [57]	(3010) [42]
$t_{1/2\beta3}$	122 ± 43.8	143 ± 102	133 ± 84.4	115 ± 49.8	
(h)	(116) [36]	(124) [71]	(113) [63]	(103) [43]	

[a] n=7, One subject excluded from calculation of summary statistics (Sampling time deviation at End Of Infusion)

[b] n=4, Three subjects not included in statistical analysis for Cycle 1 (20 mg/m^2) since they were analyzed at Cycle 2 (25 mg/m^2)

[c] n=4, One subject excluded from statistical analysis since the dose was decreased to 15 mg/m^2

AUC: area under the plasma concentration versus time curve, AUC_{last}: area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the last measurable concentration, AUC_{0-72}: area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to 72 hours post dose; BSA: body surface area; CL: total body clearance; C_{max}: maximum plasma concentration;$t_{1/2\beta3}$: half- life of the third phase considered as the elimination half-life; $t/_{12z}$: terminal half-life; V_{ss}: volume at steady state.

The effect of renal impairment on cabazitaxel PK parameters was evaluated in patients with moderate and severe renal impairment in comparison to patients with normal renal function.

For primary parameters, linear regression analysis showed no meaningful increase in cabazitaxel dose normalized exposure, ie, AUC (p=0.5961), AUC_{last} (p=0.8354), and AUC_{0-72} (p=0.5348), and no meaningful decrease in cabazitaxel clearance normalized by BSA (p=0.6268) with decrease in CrCl over the range of 101 to 8.03 mL/min.

The respective slope estimates for AUCs were close to 0 (range -0.07 to -0.03) with 90% CI containing the 0 value. The resulting geometric mean ratio estimate of AUC for patients with severe renal impairment (CrCl 15 mL/min) versus controls was 1.14 with 90% CI (0.76-1.71), indicating no significant impact of renal impairment. The same conclusion was reached for AUC_{0-72} and AUC_{last}. For CL normalized by BSA, the slope estimate was 0.06 with 90% CI (-0.15 - 0.28), leading to a geometric mean ratio estimate of 0.89 with 90% CI (0.61-1.32) for patients with severe renal impairment (CrCl 15 mL/min) versus controls. The predicted cabazitaxel CL for patients with severe renal impairment (CrCl 15 mL/min) was 26.66 L/h/m^2 versus 29.81 L/h/m^2 for controls and was thus accounting for a maximal decrease of 10.6 % in cabazitaxel CL, indicating no meaningful change with renal impairment. Results and conclusions are similar to the sensitivity test analysis, where CrCl changes during the time course of the study were taken into account.

The estimated unbound fraction of cabazitaxel was around 5.4, and no meaningful effect of the CrCl on the unbound fraction of cabazitaxel was observed. Unbound drug PK analysis would therefore lead to the same conclusion as for total drug.

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