Clinical trial results:
A Phase I/II Study of Cabazitaxel Combined with Abiraterone Acetate and Prednisone in Patients with Metastatic Castrate-Resistant Prostate Cancer (mCRPC) whose Disease has Progressed after Docetaxel Chemotherapy

Summary

EudraCT number	2011-001506-96
Trial protocol	GB
Global end of trial date	09 December 2014

Results information

Result version number	v1 (current)
This version publication date	17 July 2016
First version publication date	17 July 2016

Trial information

Trial identification

Sponsor protocol code	TCD12128

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01511536
WHO universal trial number (UTN)	U1111-1121-6324

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1 part: To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of cabazitaxel administered as a 1-hour infusion every 3 weeks in combination with oral daily abiraterone acetate and prednisone in subjects with mCRPC.
Phase 2 part: To estimate the activity of cabazitaxel in combination with abiraterone acetate and prednisone in terms of prostate-specific antigen (PSA) Response Rate.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	28 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	37
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 2 centers in phase 1 part and 3 centers in phase 2 part between March 2012 and April 2014.

Pre-assignment

Screening details:

Phase I was a dose escalation part of Cabazetaxel, administered with a constant dose of abiraterone, to determine maximally tolerated dose. Phase 2 was efficacy and safety evaluation of Cabazetaxel at a dose, determined in Phase 1,in combination with abiraterone. Cancer progression, adverse event and consent withdrawal were considered as completed.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg

Arm description:

Cabazitaxel 20 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cabazitaxel 20 mg/m^2 intravenous (IV) infusion over 1 hour on Day 1 of each 21-day cycle.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 tablets of Abiraterone acetate 250 mg orally once daily.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg orally twice daily.

Arm title	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg

Arm description:

Cabazitaxel 25 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease, progression, unacceptable toxicity or consent withdrawal.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cabazitaxel 25 mg/m^2 IV infusion over 1 hour on Day 1 of each 21-day cycle.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 tablets of Abiraterone acetate 250 mg orally once daily.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg orally twice daily.

Arm title	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg

Arm description:

Cabazitaxel at MTD as determined in phase 1 part (25 mg/m^2) on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cabazitaxel 25 mg/m^2 IV infusion over 1 hour on Day 1 of each 21-day cycle.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 tablets of Abiraterone acetate 250 mg orally once daily.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg orally twice daily.

Number of subjects in period 1	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg
Started	3	7	27
Completed	3	6	18
Not completed	0	1	9
Unspecified	-	1	9

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg
Reporting group description:	
Cabazitaxel 20 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.	
Reporting group title	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg
Reporting group description:	
Cabazitaxel 25 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease, progression, unacceptable toxicity or consent withdrawal.	
Reporting group title	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg
Reporting group description:	
Cabazitaxel at MTD as determined in phase 1 part (25 mg/m^2) on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.	

Reporting group values	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg
Number of subjects	3	7	27
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	71	60	67.1
standard deviation	± 7	± 10	± 5.4
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	3	7	27

Reporting group values	Total		
Number of subjects	37		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	0		
Male	37		

End points

End points reporting groups

Reporting group title	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg

Reporting group description:

Cabazitaxel 20 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Reporting group title	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg

Reporting group description:

Cabazitaxel 25 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease, progression, unacceptable toxicity or consent withdrawal.

Reporting group title	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg

Reporting group description:

Cabazitaxel at MTD as determined in phase 1 part (25 mg/m^2) on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Subject analysis set title	Phase 1: Overall Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Cabazitaxel 20 or 25 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Primary: Phase 1: MTD of Cabazitaxel in Combination With Abiraterone Acetate

End point title	Phase 1: MTD of Cabazitaxel in Combination With Abiraterone Acetate[1]

End point description:

MTD: highest dose level of cabazitaxel in combination with abiraterone acetate at which no more than 1 subject experienced DLT. DLT: any of events related to study drug:1) Grade 3/4 non-hematological related adverse event (AE) with exception of Grade 3 fever without documented infection;Grade 3 nausea,vomiting, or diarrhea in absence of effective maximal therapy;and Grade 3 hypersensitivity reaction in absence of required premedication. 2) Hematological toxicity: Febrile neutropenia (fever of unknown origin ≥38.5°C with neutropenia Grade 3/4);Neutropenia Grade 4 lasting >7 days;Thrombocytopenia Grade 4 or Grade 3 complicated by hemorrhage. 3) Re-treatment delay of >2 weeks due to delayed recovery from a toxicity related to study treatment to baseline or ≤ Grade 1(except for alopecia). Grades were based on NCICTC for AEs v4.03. DLT evaluable population: all subjects who received first 2 cycles,unless they discontinued study drug during first 2 cycles for DLT.

End point type	Primary

End point timeframe:

Up to Cycle 2 of Phase 1 (up to 42 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	Phase 1: Overall Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: mg/m^2				
number (not applicable)	25			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Subjects With Prostate Specific Antigen (PSA) Response

End point title	Phase 2: Percentage of Subjects With Prostate Specific Antigen (PSA) Response[2][3]

End point description:

PSA response was defined as ≥50% decrease from baseline in serum PSA levels, confirmed at least 3 weeks later. Increases of any magnitude during the first 12 weeks were ignored in determining PSA response. PSA was to be measured at baseline, every 3 weeks, thoughout study period, until progression. PSA progression was defined as: -An increase of 25% above the nadir (at least 2 ng/mL), confirmed by a second PSA value at least 3 weeks apart, in subjects who have achieved a ≥50% decline of PSA. -An increase in PSA by 25 % above the baseline level (at least 2 ng/mL), confirmed by a second PSA value at least 3 weeks apart, in subjects who have not achieved a ≥50% decline of PSA. Analysis was performed on efficacy/activity population included all subjects who had received at least 2 cycles of the study drug in Phase 2, and had a baseline and at least one post-baseline assessment for the efficacy variable of interest.

End point type	Primary

End point timeframe:

Baseline, every 3 weeks up to PSA progression (maximum duration: 603 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since analysis is descriptive in nature, statistical data could not be provided.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percentage of subjects				
number (confidence interval 95%)	46.2 (26.6 to 66.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Objective Progression Free Survival (PFS)

End point title	Phase 2: Objective Progression Free Survival (PFS)[4]

End point description:

Objective PFS was defined as time interval between date of enrollment and first occurrence of any of events:1) Radiological tumor progression (assessed using Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) was defined as at least a 20 % increase in sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since treatment started or appearance of one or more new lesions and/or unequivocal progression of existing non target-lesions. in case of progressive disease (PD) diagnosed only on non target bone lesions on bone scan, PD was to be considered only in case of appearance of at least 2 new lesions on bone scan confirmed 6 weeks later by another bone scan, and at least the appearance of 2 new additional lesions. 2) Death due to any cause. Analysis was performed by Kaplan-Meier method. Analysis was performed on efficacy/activity population. Here, 99999 represents data was not calculable as <50% subjects had event of interest.

End point type	Secondary

End point timeframe:

From baseline until radiological tumor or disease progression or death due to any cause, assessed up to Month 5

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: PSA Progression Free Survival

End point title	Phase 2: PSA Progression Free Survival[5]

End point description:

Prostate-specific antigen progression-free survival was defined as the time interval between the date of treatment start and the date of either first documented PSA progression or death due to any cause, whichever was earlier. PSA was to be measured at baseline, every 3 weeks, thoughout study period, until progression. PSA progression was defined as: -An increase of 25% above the nadir (at least 2 ng/mL), confirmed by a second PSA value at least 3 weeks apart, in subjects who have achieved a ≥50% decline of PSA. -An increase in PSA by 25 % above the baseline level (at least 2 ng/mL), confirmed by a second PSA value at least 3 weeks apart, in subjects who have not achieved a ≥50% decline of PSA. Analysis was performed by Kaplan Meire method. Analysis was performed on efficacy/activity population.

End point type	Secondary

End point timeframe:

Baseline, every 3 weeks up to PSA progression (maximum duration: 603 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: months				
median (confidence interval 95%)	6.93 (4.14 to 10.251)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Subjects With Objective Response

End point title	Phase 2: Percentage of Subjects With Objective Response[6]

End point description:

Objective response was defined as having complete response (CR) or Partial Response (PR) assessed by RECIST 1.1. CR was defined as disappearance of all target, non-target lesions; normalization of tumor marker level and all lymph nodes size was <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters). Efficacy/activity population. Number of subjects analyzed=subjects with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Baseline, every 12 weeks there after until disease progression (maximum duration: 603 days)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of subjects				
number (confidence interval 95%)	21.4 (4.7 to 50.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival

End point title	Phase 2: Overall Survival[7]

End point description:

Overall survival was defined as the time interval from the date of treatment start to the date of death due to any cause. In absence of confirmation of death, survival time was censored at the earlier of the last date the subject was known to be alive and the study cut-off date. Analysis was performed by

Kaplan-Meier method. Analysis was performed on efficacy/activity population. Here, 99999 represents data was not calculable as <50% subjects had event of interest.

End point type	Secondary

End point timeframe:

From baseline up to death or study cut-off (maximum duration: 603 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Cabazitaxel : Maximum Plasma Concentration Observed (Cmax)

End point title	Phase 2: Pharmacokinetic of Cabazitaxel : Maximum Plasma Concentration Observed (Cmax)[8]

End point description:

Analysis was performed on pharmacokinetic (PK) population which included all subjects who received at least 1 treatment. Pre-dose samples from 3 subjects of Phase 2, were above lower limit of quantification (LLOQ) (1.00 ng/mL). Hence, those subjects were excluded from analysis.

End point type	Secondary

End point timeframe:

5 minutes before cabazitaxel infusion; at end of cabazitaxel infusion; 0.25 hours post-cabazitaxel infusion; any time between 1 to 4 hours, between 6 to 24 hours, between 48 to 96 hours post cabazitaxel infusion on Day 1-Cycle 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)	330 (± 187)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Cabazitaxel : Area Under the Plasma Concentration Versus Time Curve (AUC)

End point title	Phase 2: Pharmacokinetic of Cabazitaxel : Area Under the Plasma Concentration Versus Time Curve (AUC)[9]

End point description:

Area under the concentration-time curve calculated using the following equation: AUC = Plasma clearance (CL)/dose. Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

5 minutes before cabazitaxel infusion; at end of cabazitaxel infusion; 0.25 hours post-cabazitaxel infusion; any time between 1 to 4 hours, between 6 to 24 hours, between 48 to 96 hours post cabazitaxel infusion on Day 1-Cycle 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng*h/mL				
arithmetic mean (standard deviation)	817 (± 117)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Cabazitaxel : Terminal Half-life (t 1/2z)

End point title	Phase 2: Pharmacokinetic of Cabazitaxel : Terminal Half-life (t 1/2z)[10]

End point description:

Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

5 minutes before cabazitaxel infusion; at end of cabazitaxel infusion; 0.25 hours post-cabazitaxel infusion; any time between 1 to 4 hours, between 6 to 24 hours, between 48 to 96 hours post cabazitaxel infusion on Day 1-Cycle 1

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: hour				
arithmetic mean (standard deviation)	91.6 (± 62.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Cabazitaxel : Total Plasma Clearance (CL)

End point title	Phase 2: Pharmacokinetic of Cabazitaxel : Total Plasma Clearance (CL)[11]

End point description:

Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

5 minutes before cabazitaxel infusion; at end of cabazitaxel infusion; 0.25 hours post-cabazitaxel infusion; any time between 1 to 4 hours, between 6 to 24 hours, between 48 to 96 hours post cabazitaxel infusion on Day 1-Cycle 1

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: L/h/m^2				
arithmetic mean (standard deviation)	31.4 (± 4.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Cabazitaxel : Volume of Distribution at

Steady State (Vss)

End point title	Phase 2: Pharmacokinetic of Cabazitaxel : Volume of Distribution at Steady State (Vss)[12]

End point description:

Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

5 minutes before cabazitaxel infusion; at end of cabazitaxel infusion; 0.25 hours post-cabazitaxel infusion; any time between 1 to 4 hours, between 6 to 24 hours, between 48 to 96 hours post cabazitaxel infusion on Day 1-Cycle 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: L/m^2				
arithmetic mean (standard deviation)	2711 (± 2493)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Abiraterone : Maximum Plasma Concentration Observed (Cmax)

End point title	Phase 2: Pharmacokinetic of Abiraterone : Maximum Plasma Concentration Observed (Cmax)[13]

End point description:

Analysis was performed on PK population. One subject was excluded from analysis due to aberrant data.

End point type	Secondary

End point timeframe:

0 hour (before abiraterone administration); 1, 2, 4, 6, 8, 12, 24 hours post abiraterone administration on Day 1-Cycle 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/mL				

arithmetic mean (standard deviation)	216 (± 152)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Abiraterone : First Time to Reach Cmax (Tmax)

End point title	Phase 2: Pharmacokinetic of Abiraterone : First Time to Reach Cmax (Tmax)[14]

End point description:

Analysis was performed on PK population. One subject was excluded from analysis due to aberrant data.

End point type	Secondary

End point timeframe:

0 hour (before abiraterone administration); 1, 2, 4, 6, 8, 12, 24 hours post abiraterone administration on Day 1-Cycle 1

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: hour				
median (full range (min-max))	2 (1 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Abiraterone : Area Under the Plasma Concentration Versus Time Curve From Time 0 to 24 Hours (AUC 0-24)

End point title	Phase 2: Pharmacokinetic of Abiraterone : Area Under the Plasma Concentration Versus Time Curve From Time 0 to 24 Hours (AUC 0-24)[15]

End point description:

Analysis was performed on PK population. One subject was excluded from analysis due to aberrant data.

End point type	Secondary

End point timeframe:

0 hour (before abiraterone administration); 1, 2, 4, 6, 8, 12, 24 hours post abiraterone administration on Day 1-Cycle 1

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng*h/mL				
arithmetic mean (standard deviation)	928 (± 466)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic of Abiraterone : Concentration Observed Just Before Treatment Administration During Repeated Dosing at Steady State (Ctrough ss)

End point title	Phase 2: Pharmacokinetic of Abiraterone : Concentration Observed Just Before Treatment Administration During Repeated Dosing at Steady State (Ctrough ss)[16]

End point description:

Analysis was performed on PK population. One subject was excluded from analysis due to aberrant data.

End point type	Secondary

End point timeframe:

Pre abiraterone dose on Day 1 of Cycle 1

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is reporting data for phase 2 only.

End point values	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/mL				
arithmetic mean (standard deviation)	9.99 (± 13)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (603 days) regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported AEs & deaths are treatment-emergent that is AEs that developed/worsened & deaths that occurred during 'on treatment period' (time from first dose of study drug [cabazitaxel/abiraterone, whichever came first] to last dose of study drug [cabazitaxel or abiraterone, whichever came last] + 30 days). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg

Reporting group description:

Cabazitaxel 20 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Reporting group title	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg

Reporting group description:

Cabazitaxel 25 mg/m^2 on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease, progression, unacceptable toxicity or consent withdrawal.

Reporting group title	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg

Reporting group description:

Cabazitaxel at MTD as determined in phase 1 part (25 mg/m^2) on Day 1 of each 21-day cycle in combination with abiraterone acetate 1000 mg once daily and prednisone 5 mg twice daily until disease progression, unacceptable toxicity or consent withdrawal.

Serious adverse events	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 7 (57.14%)	21 / 27 (77.78%)
number of deaths (all causes)	0	0	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Cell Lung Cancer			

subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrioventricular Block			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Cord Compression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	4 / 27 (14.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure Acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary Retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coccydynia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain In Extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device Related Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parasitic Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia Bacterial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Spinal Cord Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	4 / 27 (14.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 1: Cabazitaxel 20 mg/m^2 + Abiraterone 1000 mg	Phase 1: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg	Phase 2: Cabazitaxel 25 mg/m^2 + Abiraterone 1000 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	7 / 7 (100.00%)	27 / 27 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic Keratosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	2 / 27 (7.41%)
occurrences (all)	0	2	2
Hot Flush			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	0	1	4
Asthenia			
subjects affected / exposed	2 / 3 (66.67%)	3 / 7 (42.86%)	16 / 27 (59.26%)
occurrences (all)	2	3	17
Granuloma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Oedema Peripheral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	4 / 27 (14.81%)
occurrences (all)	1	1	5
Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences (all)	2	0	3
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	4 / 27 (14.81%)
occurrences (all)	1	1	4
Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	11 / 27 (40.74%)
occurrences (all)	0	2	11
Dyspnoea Exertional			

subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	2
Pleural Effusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	3
Psychiatric disorders			
Affective Disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Blood Bilirubin Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Blood Potassium Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Transaminases Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Weight Decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	13 / 27 (48.15%)
occurrences (all)	0	2	13
Weight Increased			

subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	4 / 27 (14.81%)
occurrences (all)	0	2	4
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	3
Hyperaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	4 / 27 (14.81%)
occurrences (all)	1	0	4
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	3 / 27 (11.11%)
occurrences (all)	1	2	3
Abdominal Pain Upper			
subjects affected / exposed	2 / 3 (66.67%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Anal Fissure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 3 (66.67%)	2 / 7 (28.57%)	6 / 27 (22.22%)
occurrences (all)	3	2	7
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	3 / 7 (42.86%)	15 / 27 (55.56%)
occurrences (all)	3	3	15
Dry Mouth			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	5 / 27 (18.52%)
occurrences (all)	0	0	5
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	1 / 27 (3.70%)
occurrences (all)	0	2	1
Gastrointestinal Hypermotility			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal Motility Disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Haemorrhoids			

subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Lip Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	5 / 7 (71.43%)	14 / 27 (51.85%)
occurrences (all)	1	5	15
Rectal Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	5 / 27 (18.52%)
occurrences (all)	1	2	5
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	6 / 27 (22.22%)
occurrences (all)	0	0	6
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	5 / 27 (18.52%)
occurrences (all)	1	2	5
Hair Disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Intertrigo			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nail Ridging			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Onycholysis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Haematuria			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	8 / 27 (29.63%)
occurrences (all)	1	2	8
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Back Pain			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	9 / 27 (33.33%)
occurrences (all)	1	2	9
Flank Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Muscle Spasms			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Musculoskeletal Pain			

subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	4 / 27 (14.81%)
occurrences (all)	1	1	4
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Neck Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Pain In Extremity			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Oral Candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Oral Fungal Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Tinea Pedis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Urinary Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	3
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	13 / 27 (48.15%)
occurrences (all)	1	1	13
Dehydration			

subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	7 / 27 (25.93%)
occurrences (all)	0	1	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2011	Following changes were made: - To add clarity and consistency to study procedures and flowchart. - To provide additional information for pharmacokinetic handling procedure, bioanalytical method, and biomarker analysis.
29 May 2012	Following changes were made: - To change the definition of DLT observation period to the first 2 cycles instead of just Cycle 1. - To amend inclusion/exclusion criteria, to adapt for changing definition of antiandrogen treatment. - To add exclusion criterion, in order to comply with the Medicines and Healthcare products Regulatory requirements for exclusion of subjects with reproductive potential who do not agree with the contraception protocol requirements. - To add analysis of RNA to the exploratory biomarker analysis. - To clarify the rules for granulocyte-colony stimulating factor prophylactic use during first two cycles. - To clarify the definition for prostate-specific antigen progression free survival secondary endpoint. - To clarify MTD confirmation. - To clarify the lower limit of dose reduction and the rules for dose reduction. - To clarify the definition of permitted/not permitted concomitant palliative radiation. - To clarify the extent of CT imaging for the evaluation of disease response/progression during the study.
17 December 2012	Following changes were made: - To change the inclusion/exclusion criteria in order to adapt to the most current clinical practice, and to address the change in subjects population in the Phase 2 part of the study. - To amend the PK sampling schedule for the Phase 2 part to adhere to a more appropriate schedule. - To modify study flowcharts to account for differences between the Phase 1 part and Phase 2 part. - To clarify the SAE reporting timeframe (24 hours instead of 1 business day).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported