ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 06/14/2012

ClinicalTrials.gov ID: NCT00659438

Study Identification

Unique Protocol ID:	D4200C00080
Brief Title:	Efficacy and Safety of Zactima™ in Patients With Castration-refractory Metastatic Prostate Cancer
Official Title:	A Randomized, Double-blind Phase II Trial to Assess the Efficacy and Safety of Bicalutamide (Casodex®) Associated to ZD6474 (Zactima™) or to Placebo in Patients With Castration-refractory Metastatic Prostate Cancer Without Any Clinical Symptom Related to Disease Progression
Secondary IDs:	

Study Status

Record Verification:	June 2012
Overall Status:	Completed
Study Start:	February 2008
Primary Completion:	November 2010 [Actual]
Study Completion:	July 2011 [Actual]

Sponsor/Collaborators

Sponsor:	AstraZeneca
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 2007-001891-35 Board Name: Comité de Protection des Personnes Ile de France VII Board Affiliation: Comité de Protection des Personnes Ile de France VII Phone: +33.1.45.21.28.46 Email: cpp.idf.7-bicetre@wanadoo.fr
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)

Study Description

Brief Summary:	This randomized, double-blind phase II trial is to assess the efficacy and safety of bicalutamide (Casodex®) associated to ZD6474 (Zactima™) or to placebo in patients with castration-refractory metastatic prostate cancer without any clinical symptom related to disease progression. The study is blinded, and subjects will be randomised (1:1 ratio) to either ZD6474 300 mg or placebo. The blinded design ensures robust, unbiased data collection and assessment. Placebo control is necessary to ensure a robust assessment of PSA PFS, and is acceptable in this subject population where all subjects will also received bicalutamide 150 mg o.d. Subjects will continue study treatment until they reach objective biological disease progression or unacceptable toxicity or withdrawal of consent or until end of trial (which event occurs first). The end of study is fixed 12 months after the last randomised patient’s first dose of study treatment.
Detailed Description:	

Conditions

Conditions:	Prostate Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment

Number of Arms:	2
Masking:	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Efficacy Study
Enrollment:	110 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1 Bicalutamide 150mg + ZD6474 300mg	Drug: ZD6474 (Vandetanib) 300mg orally, once daily Other Names: • Zactima Drug: Bicalutamide 150mg orally, once daily Other Names: • Casodex
Placebo Comparator: 2 Bicalutamide 150mg + placebo	Drug: Bicalutamide 150mg orally, once daily Other Names: • Casodex Drug: Placebo orally, once daily

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Male
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- Males presented with a confirmed histological diagnosis of adenocarcinoma of the prostate with evidence of metastases (including bone, lymph nodes, or other site) radiologically or histologically documented and despite a serum testosterone ≤1.73 nmol/L (50 ng/dL) proving castration, evidence of biochemical progression of prostate cancer, documented by a rise in PSA .

Exclusion Criteria:

- Radiotherapy or surgery or antiandrogens (except LHRH analogue) or bilateral orchiectomy within the 30 days preceding Visit 1. Incompletely healed surgical incision.
- Concomitant anticancer therapy other than surgical castration or continuous medical castration.
- Biology restriction.
- Clinical significant cardiovascular event or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.
- History of arrhythmia which is symptomatic or requires treatment (CTCAE grade 3), symptomatic despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled on medication are permitted.
- Hypertension not controlled by medical therapy
- ECG /QTc prolongation
- Presence of left bundle branch block (LBBB).

Contacts/Locations

Study Officials:

Locations: France

Research Site
Bordeaux Cedex, France

Research Site
Creteil, France

Research Site
Paris, France

Research Site
Reims Cedex, France

Research Site
Villejuif, France

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	From February 4th, 2008 to April 26th, 2010, 8 centres located in France enrolled 110 patients in the study. Among these 110 patients, 95 patients were randomized to receive either bicalutamide 150 mg + vandetanib 300 mg once daily oral dose or bicalutamide 150 mg + placebo. Last patient, last visit occurred on July 7th, 2011.
Pre-Assignment Details	Wash out of antiandrogens, within 4 weeks of randomisation to the study (at the exception of LHRH analogue, LHRH analogue had to be maintained) or within 6 weeks of randomisation to the study for bicalutamide.

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Overall Study

	Vandetanib	Placebo
Started	47	48
Assessable Set : Primary Analysis	44	45
Secondary Analysis Set	47	48
Safety Analysis Set	48 [1]	47
Completed	33	40
Not Completed	14	8
Withdrawal by Subject	2	2
Death	11	6
Lost to Follow-up	1	0

[1] One patient randomized to placebo was accounted in vandetanib group as he mistakenly received drug

Baseline Characteristics

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Baseline Measures

	Vandetanib	Placebo	Total
Number of Participants	47	48	95
Age, Continuous [units: years] Mean (Standard Deviation)	70.77 (7.68)	72.23 (6.92)	71.51 (7.30)
Gender, Male/Female [units: Participants]			
Female	0	0	0
Male	47	48	95

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Prostate Specific Antigen (PSA) Progression Free Rate at 4 Months
Measure Description	To assess the effect of vandetanib on biological progression free rate based on PSA level (assessable set). PSA progression free rate defined as the number of participants with : • After decline from baseline: a 25% increase above the nadir • No decline from baseline: a 25% increase above the baseline (min. increase of 2 ng/mL)
Time Frame	4 months
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	44	45
Prostate Specific Antigen (PSA) Progression Free Rate at 4 Months [units: Participants]	8	7

2. Secondary Outcome Measure:

Measure Title	Progression Free Survival (PFS) at 4 Months (Instead of Time to PSA Progression)
Measure Description	Due to the difficulties to assess biological progression date when clinical progression has occurred first, and because of the non-assessment of the clinical progression after treatment discontinuation, Time to PSA progression was not evaluated. PFS was evaluated instead, whether biological or clinical progression.
Time Frame	4 months
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	47	48
Progression Free Survival (PFS) at 4 Months (Instead of Time to PSA Progression) [units: weeks]	12.2 (11.8 to 12.4)	12.8 (12.2 to 13.6)

	Vandetanib	Placebo
Median (95% Confidence Interval)		

3. Secondary Outcome Measure:

Measure Title	Progression Free Survival (PFS) at 4 Months (Instead of Time to Onset of Cancer-related Symptoms)
Measure Description	Due to the difficulties to assess biological progression date when clinical progression has occurred first, and because of the non-assessment of the clinical progression after treatment discontinuation, Time to onset of cancer-related symptoms was not evaluated. PFS was evaluated instead, whether biological or clinical progression.
Time Frame	4 months
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	47	48
Progression Free Survival (PFS) at 4 Months (Instead of Time to Onset of Cancer-related Symptoms) [units: weeks] Median (95% Confidence Interval)	12.2 (11.8 to 12.4)	12.8 (12.2 to 13.6)

4. Secondary Outcome Measure:

Measure Title	PSA Response Rate

Measure Description	To investigate the effect of vandetanib on the PSA response rate. PSA response rate defined by the number of participants with a PSA decrease relative to baseline of at least 50%. A minimum decrease of 2 ng/mL in absolute value and a confirmation on at least 2 consecutive occasions (at least 4 weeks apart) were requested.
Time Frame	4 months
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	47	48
PSA Response Rate [units: Participants]	3	5

5. Secondary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	To investigate the effect of vandetanib on overall survival. Patients alive at the time of the statistical analysis were censored at the time they were last known to be alive. Due to censored data, median overall survival in the placebo group cannot be calculated. OS defined as the number of participants who were alive.
Time Frame	End of study (July 2011)
Safety Issue?	No

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	47	48
Overall Survival (OS) [units: participants]	32	35

6. Secondary Outcome Measure:

Measure Title	Progression Rate From the Radionuclide Bone Scanning
Measure Description	To describe the effect of vandetanib on progression rate from the radionuclide bone scanning in a sub-group of patients who had a bone scan within 3 to 6 months after 1st treatment dose. Number of participants with at least 2 new lesions on the radionuclide bone scan compared to baseline assessment were counted for calculation of progression rate.
Time Frame	4 months
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	10	13
Progression Rate From the Radionuclide Bone Scanning [units: Participants]	3	4

7. Secondary Outcome Measure:

Measure Title	Number of Circulating Tumour Cells (CTC) (in Patients Included in Ile de France Centres Only)
Measure Description	To investigate the effect of vandetanib on CTC. Numbering of CTCs to be performed at baseline, 1 week, 1 and 2 months after randomisation. This study was proposed only to patients followed in a study centre located in Ile de France. Correlation between the number of CTCs and PSA response was to be estimated after 1 week, 1 and 2 months of treatment
Time Frame	4 months
Safety Issue?	No

Analysis Population Description

This part of the study was proposed only to patients followed in one study centre located in Ile de France and finally no blood sample has been taken at this centre. So no data on CTCs, CECs were collected and no analysis was performed.

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

8. Secondary Outcome Measure:

Measure Title	Number of Circulating Endothelial Cells (CEC) of Tumour Blood Cells (in Patients Included in Ile de France Centres Only)
Measure Description	To investigate the effect of vandetanib on CEC. Numbering of CECs was to be performed at baseline, 1 week, 1 month and 2 months after randomisation. Correlation between the number of CECs and PSA response was to be estimated after 1 week, 1 month and 2 months of treatment.
Time Frame	4 months

Safety Issue?	No

Analysis Population Description

This part of the study was proposed only to patients followed in one study centre located in Ile de France and finally no blood sample has been taken at this centre. So no data on CTCs, CECs were collected and no analysis was performed.

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

9. Secondary Outcome Measure:

Measure Title	Number of Patients With CECs, CTCs and Gene Signature Profile of CTCs
Measure Description	To investigate the relationship between response to vandetanib, CTCs and CECs. To investigate gene signature profile of antiangiogenic response by gene micro-array analysis of CTCs. Gene signature profile of CTCs was aimed to be compared before and after 2 months of treatment. No blood sample has been taken for the study, and so results on CTCs, CECs of tumour vessels and gene and signature profiles of CTCs were not performed.
Time Frame	4 months
Safety Issue?	No

Analysis Population Description

[Not Specified]

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Measured Values

	Vandetanib	Placebo
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	Safety analysis set is composed with all randomized subjects who received at least one dose of treatment. One patient mistakenly received vandetanib during 3 days while randomized to placebo. This patient was accounted in the vandetanib group in the safety population. So, safety analysis set is composed with 48 Vandetanib and 47 placebo patients.

Reporting Groups

	Description
Vandetanib	Bicalutamide 150mg + Vandetanib (ZD6474) 300mg
Placebo	Bicalutamide 150mg + placebo

Serious Adverse Events

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	17/48 (35.42%)	4/47 (8.51%)
Blood and lymphatic system disorders		
Anaemia [A] *	1/48 (2.08%)	0/47 (0%)
Febrile bone marrow aplasia [A] *	0/48 (0%)	1/47 (2.13%)
Cardiac disorders		
Torsade de pointes [A] *	1/48 (2.08%)	0/47 (0%)
Ventricular extrasystoles [A] *	1/48 (2.08%)	0/47 (0%)
Gastrointestinal disorders		
Anal fissure [A] *	1/48 (2.08%)	0/47 (0%)

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Ileus [A] *	1/48 (2.08%)	0/47 (0%)
Intestinal obstruction [A] *	0/48 (0%)	1/47 (2.13%)
General disorders		
Death [A] *	1/48 (2.08%)	0/47 (0%)
Disease progression [A] *	1/48 (2.08%)	0/47 (0%)
Performance status decrease [A] *	1/48 (2.08%)	0/47 (0%)
Infections and infestations		
Bronchopneumonia [A] *	1/48 (2.08%)	0/47 (0%)
Pneumonia [A] *	1/48 (2.08%)	0/47 (0%)
Sepsis [A] *	1/48 (2.08%)	0/47 (0%)
Septic shock [A] *	0/48 (0%)	1/47 (2.13%)
Injury, poisoning and procedural complications		
Ankle fracture [A] *	0/48 (0%)	1/47 (2.13%)
Investigations		
Electrocardiogram QT prolonged [A] *	2/48 (4.17%)	0/47 (0%)
Musculoskeletal and connective tissue disorders		
Back pain [A] *	0/48 (0%)	1/47 (2.13%)
Spondylitis [A] *	1/48 (2.08%)	0/47 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Chronic lymphocytic leukaemia [A] *	1/48 (2.08%)	0/47 (0%)
Prostate cancer [A] *	0/48 (0%)	1/47 (2.13%)
Nervous system disorders		
Cerebral haemorrhage [A] *	1/48 (2.08%)	0/47 (0%)

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Cerebrovascular accident [A] *	2/48 (4.17%)	0/47 (0%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism [A] *	1/48 (2.08%)	0/47 (0%)
Skin and subcutaneous tissue disorders		
Drug eruption [A] *	1/48 (2.08%)	0/47 (0%)
Photosensitivity reaction [A] *	2/48 (4.17%)	0/47 (0%)
Rash erythematous [A] *	1/48 (2.08%)	0/47 (0%)
Toxic skin eruption [A] *	1/48 (2.08%)	0/47 (0%)
Surgical and medical procedures		
Stent placement [A] *	1/48 (2.08%)	0/47 (0%)
Vascular disorders		
Hypertension [A] *	1/48 (2.08%)	0/47 (0%)
Hypertensive crisis [A] *	1/48 (2.08%)	0/47 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	47/48 (97.92%)	47/47 (100%)
Gastrointestinal disorders		
Abdominal pain [A] †	4/48 (8.33%)	3/47 (6.38%)
Abdominal pain upper [A] †	3/48 (6.25%)	1/47 (2.13%)
Constipation [A] †	8/48 (16.67%)	8/47 (17.02%)

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Diarrhoea [A] †	21/48 (43.75%)	5/47 (10.64%)
Nausea [A] †	9/48 (18.75%)	0/47 (0%)
General disorders		
Asthenia [A] †	20/48 (41.67%)	19/47 (40.43%)
Chest pain [A] †	0/48 (0%)	3/47 (6.38%)
Fatigue [A] †	2/48 (4.17%)	3/47 (6.38%)
Pain [A] †	0/48 (0%)	3/47 (6.38%)
Hepatobiliary disorders		
Cytolytic hepatitis [A] †	4/48 (8.33%)	0/47 (0%)
Infections and infestations		
Rhinitis [A] †	1/48 (2.08%)	3/47 (6.38%)
Urinary tra ct infection [A] †	4/48 (8.33%)	1/47 (2.13%)
Investigations		
Electrocardiogram QT prolonged [A] †	8/48 (16.67%)	1/47 (2.13%)
Weight decreased [A] †	5/48 (10.42%)	1/47 (2.13%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	3/48 (6.25%)	7/47 (14.89%)
Back pain [A] †	7/48 (14.58%)	6/47 (12.77%)
Bone pain [A] †	2/48 (4.17%)	3/47 (6.38%)
Musculoskeletal pain [A] †	3/48 (6.25%)	5/47 (10.64%)
Myalgia [A] †	2/48 (4.17%)	4/47 (8.51%)
Pain in extremity [A] †	1/48 (2.08%)	4/47 (8.51%)
Nervous system disorders		

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Dizziness [A] †	5/48 (10.42%)	5/47 (10.64%)
Headache [A] †	3/48 (6.25%)	4/47 (8.51%)
Sciatica [A] †	3/48 (6.25%)	1/47 (2.13%)
Psychiatric disorders		
Anxiety [A] †	2/48 (4.17%)	7/47 (14.89%)
Depression [A] †	4/48 (8.33%)	0/47 (0%)
Insomnia [A] †	4/48 (8.33%)	6/47 (12.77%)
Renal and urinary disorders		
Dysuria [A] †	1/48 (2.08%)	3/47 (6.38%)
Haematuria [A] †	2/48 (4.17%)	3/47 (6.38%)
Pollakiuria [A] †	2/48 (4.17%)	3/47 (6.38%)
Reproductive system and breast disorders		
Gynaecomastia [A] †	7/48 (14.58%)	4/47 (8.51%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] †	4/48 (8.33%)	2/47 (4.26%)
Epistaxis [A] †	3/48 (6.25%)	1/47 (2.13%)
Skin and subcutaneous tissue disorders		
Dry Skin [A] †	4/48 (8.33%)	1/47 (2.13%)
Erythema [A] †	3/48 (6.25%)	1/47 (2.13%)
Photosensitivity reaction [A] †	5/48 (10.42%)	0/47 (0%)
Pruritus [A] †	4/48 (8.33%)	1/47 (2.13%)
Rash [A] †	4/48 (8.33%)	1/47 (2.13%)
Rash erythematous [A] †	3/48 (6.25%)	0/47 (0%)

	Vandetanib	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Skin fissures [A] †	3/48 (6.25%)	0/47 (0%)
Vascular disorders		
Hot flush [A] †	11/48 (22.92%)	11/47 (23.4%)
Hypertension [A] †	14/48 (29.17%)	5/47 (10.64%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

Results Point of Contact:

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