Clinical trial results:
Phase III, open-label, multi-center study to assess the pharmacodynamic (PD), pharmacokinetic (PK), and safety of Zoreline 10.8 mg goserelin subcutaneous implant (Novalon) in male patients with prostate cancer

Summary

EudraCT number	2013-000799-14
Trial protocol	BE NL
Global end of trial date	03 May 2016

Results information

Result version number	v1 (current)
This version publication date	18 August 2022
First version publication date	18 August 2022

Trial information

Trial identification

Sponsor protocol code	0080CA002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novalon S.A.
Sponsor organisation address	Rue Saint Georges 5-7, Liège, Belgium, 4000
Public contact	Clinical Study Leader , Novalon S.A., +32 43492822, Clinical.Trials@mithra.com
Scientific contact	Clinical Study Leader , Novalon S.A., +32 43492822, Clinical.Trials@mithra.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	02 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the ability of Zoreline 10.8 mg SC implant to induce by Day 29 of Cycle 1 at the latest and maintain up to Day 85 of Cycle 2 (end of treatment) testosterone plasma suppression (≤50 ng/dL) in male patients with confirmed diagnosis of prostate cancer.

This clinical study was designed to assess the pharmacodynamics (PD), pharmacokinetics (PK), and safety of the Zoreline 10.8 mg SC implant to collect data for marketing authorization application.

Zoreline was developed as a generic version of Zoladex® 10.8 mg goserelin SC implant (AstraZeneca, United Kingdom). The active pharmaceutical ingredient and excipients in Zoreline and Zoladex® are identical.

Luteinizing hormone (LH)-releasing hormone (LHRH) agonists, such as goserelin, are potential therapies for prostate cancer. With continuous administration, these agents block LH secretion and reduce testosterone concentrations to anorchid levels.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95) and with applicable local requirements.

Safety was assessed by monitoring of adverse events (AEs) volunteered, observed, and elicited by general questioning in a non-suggestive manner throughout the study. All new clinically relevant abnormalities, significant changes according to the opinion of the Investigator were reported as AEs in the case report form. Vital signs, electrocardiograms (ECGs), and clinical laboratory test results were monitored.

To assess the potential futility of the study which would have induced an early stopping of the study to avoid exposure of patients to a potentially non-efficient drug, the Independent Statistician – not involved in any other aspect of the study – was provided periodically (about every 3 months) by SGS Secure Data Office (to assure blinding of the study team) with a snapshot of the clinical database containing the available cleaned data for treatment administration, PD sampling and testosterone results at that time

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

LIST OF ABBREVIATIONS USED IN THIS STUDY ENTRY

AE=Adverse event;
AUC (0-t)=Area under the plasma drug concentration-time curve, calculated to the last quantifiable data point;
Cmax=Maximum measured plasma concentration;
Cmin=Minimum measured post-dose plasma concentration;
ECOG=Eastern Cooperative Oncology Group;
HPLC-MS/MS=High-performance liquid chromatography with tandem mass spectrometric detection;
ITT population=Included all subjects who received study medication and had at least 1 post-dose testosterone assessment. In case of drop-out or of missing testosterone assessments, the responder

status was defined as the responder status observed over all testosterone assessments available at the time of drop-out;
LH=Luteinizing hormone;
LHRH=Luteinizing hormone releasing hormone;
mITT population=Modified ITT population; included all subjects of the ITT population for whom the final responder status would not have changed due to missing testosterone assessments or due to testosterone levels >50 ng/dL in Cycle 2 between Day 2 and Day 4. This also included intermediate missing assessments and not only assessments after drop-out;
PD=Pharmacodynamics;
PK=Pharmacokinetics;
Tmax=Time until the maximum measured plasma concentration;

Actual start date of recruitment	07 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 119
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Moldova, Republic of: 14
Country: Number of subjects enrolled	Georgia: 3
Worldwide total number of subjects	142
EEA total number of subjects	125

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)	16
From 65 to 84 years	121
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Male adult subjects (18 years or older), with confirmed diagnosis of prostate adenocarcinoma were screened according to the study inclusion and exclusion criteria. In total, 163 subjects were screened and 142 subjects were randomized to treatment.

Pre-assignment

Screening details:

At the screening visit (7 to 4 days before first study treatment administration), inclusion/exclusion criteria were assessed; subjects selected to enter in the study had ECOG score of ≤ 2 measured at screening.

All subjects signed an Informed Consent Form before the first study-related procedure was performed.

Period 1

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

Blinding implementation details:

This was an open-label study.

Testosterone results remained blinded for all people involved in the clinical conduct throughout the study up to the clinical database lock for the final analysis to avoid any potential bias review of the testosterone levels.

Arms

Arm title	Treatment (Zoreline)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Zoreline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

Name : Zoreline
Formulation : Goserelin acetate
Strength of dosage form : 10.8 mg subcutaneous implant

The test product was injected every 84 days: on Day 1 of Cycle 1 and Cycle 2 (Day 85 of Cycle 1 was Day 1 of Cycle 2), into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team. The use of local anaesthetic was allowed if this was part of local practice.

Each treatment cycle lasted 84 days and the total treatment duration was 168 days. A follow-up visit was done 84 days after the last dose (Day 85 of Cycle 2).

Number of subjects in period 1	Treatment (Zoreline)
Started	142
Completed	133
Not completed	9
Adverse event, serious fatal	1
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Did not meet all selection criteria	1
Sponsor’s decision	1
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	142	142	
Age categorical			
The intent-to-treat (ITT) population was used to evaluate the demographic characteristics of the subjects.			
Units: Subjects			
Adults (18-64 years)	16	16	
From 65-84 years	121	121	
85 years and over	5	5	
Age continuous			
Units: years			
arithmetic mean	73.7		
standard deviation	± 6.62	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	142	142	
Race			
Units: Subjects			
Caucasian	142	142	
Body mass index (BMI)			
Units: kg/m²			
arithmetic mean	27.44		
standard deviation	± 3.67	-	

Subject analysis sets

Subject analysis set title	mITT set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population=Modified ITT population; included all subjects of the ITT population for whom the final responder status would not have changed due to missing testosterone assessments or due to testosterone levels >50 ng/dL in Cycle 2 between Day 2 and Day 4. This also included intermediate missing assessments and not only assessments after drop-out;

Reporting group values	mITT set		
Number of subjects	125		
Age categorical			
The intent-to-treat (ITT) population was used to evaluate the demographic characteristics of the subjects.			
Units: Subjects			
Adults (18-64 years)	13		
From 65-84 years	107		
85 years and over	5		

Age continuous Units: years arithmetic mean standard deviation	 74.2 ± 6.47		
Gender categorical Units: Subjects			
Female Male	0 125		
Race Units: Subjects			
Caucasian	125		
Body mass index (BMI) Units: kg/m² arithmetic mean standard deviation	 27.56 ±		

End points

End points reporting groups

Reporting group title	Treatment (Zoreline)
Reporting group description: -	
Subject analysis set title	mITT set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population=Modified ITT population; included all subjects of the ITT population for whom the final responder status would not have changed due to missing testosterone assessments or due to testosterone levels >50 ng/dL in Cycle 2 between Day 2 and Day 4. This also included intermediate missing assessments and not only assessments after drop-out;

Primary: 1a_Testosterone suppression in plasma -- ≤50 ng/dL (ITT set)

End point title	1a_Testosterone suppression in plasma -- ≤50 ng/dL (ITT

End point description:

Testosterone suppression in plasma to ≤50 ng/dL

A responder was defined as a subject who reached plasma testosterone levels below the castrate level (≤50 ng/dL) by Day 29 of Cycle 1 at the latest and maintained plasma testosterone levels below the castrate level (≤50 ng/dL) until Day 85 of Cycle 2 (end of treatment).

Total testosterone was measured in plasma, using high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS).

ITT population=Included all subjects who received study medication and had at least 1 post-dose testosterone assessment. In case of drop-out or of missing testosterone assessments, the responder status was defined as the responder status observed over all testosterone assessments available at the time of drop-out.

End point type	Primary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

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: The primary objective was addressed using the mITT population. The primary objective was considered as achieved if the lower limit of the 2-sided 95% CI on the responder rate was ≥90%.

A total of 105 subjects in the ITT population were responders (73.9%, 2-sided 95% CI: 65.9; 80.9%).

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	142[2]			
Units: subjects				
UNDEFINED	3			
NON-RESPONDER	34			
RESPONDER	105			

Notes:

[2] - ITT population

Statistical analyses

No statistical analyses for this end point

Primary: 1b_Testosterone suppression in plasma -- ≤50 ng/dL (mITT set)

End point title	1b_Testosterone suppression in plasma -- ≤50 ng/dL (mITT set)[3]

End point description:

Testosterone suppression in plasma to ≤50 ng/dL

A responder was defined as a subject who reached plasma testosterone levels below the castrate level (≤50 ng/dL) by Day 29 of Cycle 1 at the latest and maintained plasma testosterone levels below the castrate level (≤50 ng/dL) until Day 85 of Cycle 2 (end of treatment).

Total testosterone was measured in plasma, using high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS).

mITT Population: included all subjects of the ITT population for whom the final responder status would not have changed due to missing testosterone assessments or due to testosterone levels >50 ng/dL in Cycle 2 between Day 2 and Day 4. This also included intermediate missing assessments and not only assessments after drop-out.

End point type	Primary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

Notes:

[3] - 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: The primary objective was addressed using the mITT population. The primary objective was considered as achieved if the lower limit of the 2-sided 95% CI on the responder rate was ≥90%.

A total of 92 subjects in the mITT population were responders (73.6%; 2-sided 95% CI: 65.0; 81.1%).

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	125[4]			
Units: subjects				
UNDEFINED	0			
NON-RESPONDER	33			
RESPONDER	92			

Notes:

[4] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 2_PD_Plasma Testosterone -- Cmax

End point title	2_PD_Plasma Testosterone -- Cmax

End point description:

Cmax -- Plasma Testosterone -- Maximum measured testosterone plasma concentration.

The administered medication (Goserelin) is used to suppress production of the sex hormones, including testosterone and is used particularly in the treatment of prostate cancer.

For further details regarding measurement of testosterone concentration in plasma please see description prepared for end point # 1.

For all pharmacodynamic (PD) parameters, the results are presented for the intent-to treat (ITT)

population.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	142[5]			
Units: ng/dL				
arithmetic mean (standard deviation)	720.4 (± 230.4)			

Notes:

[5] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: 3_PD_Plasma Testosterone -- AUC(0-t), AUC (85d, Cycle 1), AUC (85d, Cycle 2)

End point title	3_PD_Plasma Testosterone -- AUC(0-t), AUC (85d, Cycle 1), AUC (85d, Cycle 2)

End point description:

AUC for plasma testosterone

AUC(0-t)=Area under the plasma concentration-time curve (AUC) from Day 1 to Day 85 in each treatment cycle, i.e. during 2 consecutive treatment cycles in which Day 85 represents the end of treatment of each cycle.

For further details regarding measurement of testosterone concentration in plasma please see description prepared for end point # 1.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	126[6]			
Units: day.ng/dL				
arithmetic mean (standard deviation)				
AUC 85d (Cycle 1) AUC 85d (Cycle 2) AUC (0-t)	9153 (± 3980) 1638 (± 1695) 10684 (± 5033)			

Notes:

[6] - N=126 (AUC85d, Cycle 1)
N=126 (AUC85d, Cycle 2)
N=118 (AUC0-t)

Statistical analyses

No statistical analyses for this end point

Secondary: 4_PD_Plasma Testosterone -- Flare

End point title	4_PD_Plasma Testosterone -- Flare

End point description:

Plasma Testosterone -- Flare

Flare is a temporary increase in testosterone levels in the body caused by certain types of hormone therapy used to treat prostate cancer.

Flare was defined as peaks at ≥2-fold the baseline testosterone level during Cycle 1 between Day 1 and Day 29. Both the number of peaks and values per subject were evaluated.

For further details regarding measurement of testosterone concentration in plasma please see description prepared for end point # 1.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	142[7]			
Units: subjects				
YES	14			
NO	128			

Notes:

[7] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 5_PD_Plasma Testosterone -- Time to achieve castration level

End point title	5_PD_Plasma Testosterone -- Time to achieve castration level

End point description:

PD_Plasma Testosterone -- Time to achieve castration level

Time to achieve castration level was defined as the time of the first testosterone value below the castrate level (≤50 ng/dL) during the entire treatment period.

For further details regarding measurement of testosterone concentration in plasma please see description prepared for end point # 1.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	141[8]			
Units: days				
arithmetic mean (standard deviation)	28.7 (± 3.38)			

Notes:

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 6_PD_Plasma Testosterone -- Surge upon reinjection

End point title	6_PD_Plasma Testosterone -- Surge upon reinjection

End point description:

PD_Plasma Testosterone -- Surge upon reinjection

Acute on chronic phenomenon (surge upon reinjection) was defined as the occurrence of testosterone level greater than 50 ng/dL during Cycle 2 between Day 2 and Day 4, following re-injection and when the pre-injection value was ≤50 ng/mL. The number of occurrences and values per subject was evaluated.

For further details regarding measurement of testosterone concentration in plasma please see description prepared for end point # 1.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	102[9]			
Units: subjects				
YES	12			
NO	90			

Notes:

[9] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 7_PD_Plasma Testosterone -- Escape or Surge

End point title	7_PD_Plasma Testosterone -- Escape or Surge

End point description:

PD_Plasma Testosterone -- Escape or Surge

Escape or surge was defined as a value of testosterone level above 50 ng/dL following the onset of suppression after the initial flare in Cycle 1 and from Day 8 to Day 85 of Cycle 2, which was not confirmed at the next sampling day.

For further details regarding measurement of testosterone concentration in plasma please see description prepared for end point # 1.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	141[10]			
Units: subjects				
YES	16			
NO	125			

Notes:

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 8_PK -- Cmax -- Plasma goserelin -- Maximum measured concentration

End point title	8_PK -- Cmax -- Plasma goserelin -- Maximum measured concentration

End point description:

Cmax: Maximum measured goserelin plasma concentration.

HPLC-MS/MS method was used for the quantification of goserelin in plasma.

Results represent Cmax observed during Cycle 1 and Cycle 2 of treatment. The number of subjects contributing to the calculated value during each cycle is shown under the results table below.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	136[11]			
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1	7979 (± 3128)			
Cycle 2	8955 (± 3333)			

Notes:

[11] - ITT Population

N=136 (Cycle 1)
N=135 (Cycle 2)

Statistical analyses

No statistical analyses for this end point

Secondary: 9_PK -- Cmin -- Plasma goserelin -- Minimum measured concentration

End point title	9_PK -- Cmin -- Plasma goserelin -- Minimum measured concentration

End point description:

PK -- Cmin -- Plasma goserelin -- Minimum measured concentration

Results represent Cmin observed during Cycle 1 and Cycle 2 of treatment.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	123[12]			
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1	49.4 (± 34.5)			
Cycle 2	74.5 (± 49.1)			

Notes:

[12] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: 10_PK -- tmax -- Plasma goserelin - Time until the maximum measured plasma concentration

End point title	10_PK -- tmax -- Plasma goserelin - Time until the maximum measured plasma concentration

End point description:

PK -- tmax -- Plasma goserelin - Time until the maximum measured plasma concentration

Results represent tmax observed during Cycle 1 and Cycle 2 of treatment. The number of subjects contributing to the calculated value during each cycle is shown under the results table below.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	136[13]			
Units: days				
median (full range (min-max))				
Cycle 1	2.0 (1.7 to 2.3)			
Cycle 2	2.0 (1.7 to 15.0)			

Notes:

[13] - ITT Population

N=136 (Cycle 1)
N=135 (Cycle 2)

Statistical analyses

No statistical analyses for this end point

Secondary: 11_PK -- AUC(85 days) -- Plasma goserelin -- Area under the plasma concentration-time curve

End point title	11_PK -- AUC(85 days) -- Plasma goserelin -- Area under the plasma concentration-time curve

End point description:

PK -- AUC(85 days) -- Plasma goserelin -- Area under the plasma concentration-time curve

Area under the plasma concentration-time curve [AUC] from Day 1 to Day 85 in each treatment cycle, i.e. during 2 consecutive treatment cycles in which Day 85 represents the end of treatment of each

End point type	Secondary

End point timeframe:

Days 1 (pre-dose, baseline), 2, 4, 8, 15, 29, 36, 57, and 85 of Cycle 1 (pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57 and 85 of Cycle 2 (end of treatment)

End point values	Treatment (Zoreline)			
Subject group type	Reporting group			
Number of subjects analysed	123[14]			
Units: day.pg/mL				
arithmetic mean (standard deviation)				
Cycle 1	32148 (± 11146)			
Cycle 2	40046 (± 13818)			

Notes:
[14] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from the time of patient informed consent signature to study completion or discontinuation.

Adverse event reporting additional description:

All AEs starting on or after the time study drug implantation were classified as treatment-emergent adverse events (TEAEs).

Safety population was used to evaluate the AEs.

The safety population included all subjects who received study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Treatment (Zoreline)

Reporting group description:

Safety population was used to evaluate the AEs.

Serious adverse events	Treatment (Zoreline)		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 142 (7.04%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myxofibrosarcoma			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery disease			

subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Treatment (Zoreline)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 142 (41.55%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	42 / 142 (29.58%)		
occurrences (all)	46		
Hypertension			
subjects affected / exposed	8 / 142 (5.63%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 142 (5.63%)		
occurrences (all)	9		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 142 (8.45%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2014	The first substantial amendment made to the original protocol included: • Withdrawal and safety follow-up visits for subjects prematurely discontinuing the study were replaced by an End of Study visit within 1 week after Day 85 of the cycle in which the subject prematurely discontinued.
06 May 2015	On 06-May-2015, a second substantial amendment was made to the original protocol included: • Inclusion criterion 7 was changed from "PSA level ≥ 4 ng/mL" to "PSA level ≥ 4 ng/mL; Exception: for patients who have had previous prostatectomy and/or prostate radiotherapy, all PSA levels are allowed." • Inclusion criterion 9 was changed. Patients enrolled into the study had to have BMI ranging between 18.5 and 35 kg/m2 (inclusive) instead of 18.5 and 32 kg/m2 (inclusive).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported