Clinical trial results:
Open-label, multi-center, randomized parallel group study to assess the pharmacokinetic (PK) profile of Zoreline 10.8 mg goserelin subcutaneous implant (test product, Novalon S.A.) and of Zoladex® LA 10.8 mg goserelin subcutaneous implant (reference product, AstraZeneca UK Limited) in male patients with prostate cancer

Summary

EudraCT number	2015-001756-30
Trial protocol	BG
Global end of trial date	08 March 2017

Results information

Result version number	v1 (current)
This version publication date	16 August 2022
First version publication date	16 August 2022

Trial information

Trial identification

Sponsor protocol code	No0002-C201

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	20 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Characterize the goserelin plasma concentration profile based on primary PK endpoints from Day 1 to 85 (1 treatment cycle, Day 85 represents the end of treatment), after injection with Zoreline 10.8 mg or Zoladex® LA 10.8 mg subcutaneous implant in male patients with prostate cancer.

Luteinizing hormone (LH)-releasing hormone (LHRH) agonists are potential therapies for prostate cancer. These agents block LH secretion and reduce testosterone concentrations to anorchid levels - a process also known as “medical orchiectomy”.

A depot preparation of a LHRH agonist, goserelin (Zoladex® LA 10.8 mg subcutaneous implant, AstraZeneca UK Limited, UK) may be administered subcutaneously every 3 months. A new formulation of goserelin (Zoreline 10.8 mg subcutaneous implant) with a similar quantitative and qualitative composition to Zoladex® was developed by Novalon S.A., Belgium. A single subcutaneous implant dose of the 2 products was evaluated in this parallel arm study.

Protection of trial subjects:

The study was conducted under the ethical principles that have their origin in the Declaration of Helsinki, the laws and regulations of the country in which the study was conducted, and the current version of the International Council on Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guidance. Appropriate procedures for coding were applied to ensure the anonymity of the subjects on all trial related documents.

Safety was assessed by the monitoring of 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, clinical laboratory test results were monitored.

Background therapy:

Background therapy -- Not applicable

Evidence for comparator:

Evidence for comparators -- Not applicable

LIST OF ABBREVIATIONS USED IN THIS STUDY ENTRY

AE=Adverse event;
AUC(0-t)=Area under the plasma concentration-time curve from administration to the last measurable concentration at time t in both groups;
AUC(0-tcom)= Area under the plasma concentration-time curve from administration to the last common measurable time-point within all patients in both groups;
BMI=Body mass index;
C(day85)=Goserelin plasma concentration at the end of the treatment period;
Cmax=Maximum measured plasma concentration;
Cmin=Minimum measured post-dose plasma concentration;
ECOG=Eastern Cooperative Oncology Group;
GLSM=Geometric least square means;
ITT=Intent-to-treat. The ITT set was composed of all subjects who received study drug and had at least 1 post-dose assessment;
LH=Luteinizing hormone;
LHRH=Luteinizing hormone releasing hormone;
tmax=Time until the maximum measured goserelin plasma concentration is reached;

PD=Pharmacodynamic;
PP=Per Protocol. The PP set included all patients of the intention-to-treat (ITT) population who completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin plasma concentrations. These included, but are not limited to, predefined not allowed concomitant medications and delayed visit schedules;
PK=Pharmacokinetic;
TEAE=Treatment-emergent adverse events;
UPLC-MS/MS=Ultra-performance liquid chromatography method with triple quadrupole tandem mass spectrometric detection;

Actual start date of recruitment	29 January 2016
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	Poland: 15
Country: Number of subjects enrolled	Bulgaria: 43
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	12
From 65 to 84 years	45
85 years and over	1

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. Overall, 58 subjects were randomized (N=29 subjects in the test treatment group and N=29 subjects in the reference group).

Pre-assignment

Screening details:

At the screening visit (4 to 14 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 prior to any study-related procedures were performed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoreline (Test product)

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 administered subcutaneously once, on Day 1 of the study, 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.

Arm title	Zoladex (Reference product)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Zoladex® LA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

Name : Zoladex® LA
Formulation: Goserelin acetate
Strength of dosage form: 10.8 mg subcutaneous implant

The reference product was administered subcutaneously once, on Day 1 of the study, 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.

Number of subjects in period 1	Zoreline (Test product)	Zoladex (Reference product)
Started	29	29
Completed	28	26
Not completed	1	3
Consent withdrawn by subject	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Zoreline (Test product)
Reporting group description: -	
Reporting group title	Zoladex (Reference product)
Reporting group description: -	

Reporting group values	Zoreline (Test product)	Zoladex (Reference product)	Total
Number of subjects	29	29	58
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	12
From 65-84 years	23	22	45
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	70.3	71.1	
standard deviation	± 6.81	± 8.29	-
Gender categorical Units: Subjects			
Male	29	29	58
ECOG scale of Performance Status			
The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis Grade: 0 – Asymptomatic. Fully active. 1 – Symptomatic, but completely ambulatory. 2 – Symptomatic, <50% in bed during the day. 3 – Symptomatic, >50% in bed, but not bedbound. 4 – Bed bound. Completely disabled. ECOG=Eastern Cooperative Oncology Group			
Units: Subjects			
Grade 0	23	21	44
Grade 1	6	7	13
Grade 2	0	1	1
Grade 3	0	0	0
Grade 4	0	0	0
Body Mass Index (BMI) Units: (kg/m2			
arithmetic mean	26.67	27.16	
standard deviation	± 3.65	± 3.58	-

Subject analysis sets	
Subject analysis set title	Zoreline (Test product) - PP set
Subject analysis set type	Per protocol

Subject analysis set description:

Included all subjects who received Zoreline (Test product), had at least 1 post-dose assessment, and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin plasma concentrations. These included, but are not limited to, predefined not allowed concomitant medications and delayed visit schedules.

Subject analysis set title	Zoladex (Reference product) - PP set
Subject analysis set type	Per protocol

Subject analysis set description:

Included all subjects who received Zoladex (Reference product), had at least 1 post-dose assessment, and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin plasma concentrations. These included, but are not limited to, predefined not allowed concomitant medications and delayed visit schedules.

Reporting group values	Zoreline (Test product) - PP set	Zoladex (Reference product) - PP set	
Number of subjects	27	24	
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	
From 65-84 years	21	17	
85 years and over		1	
Age continuous Units: years			
arithmetic mean	70.0	70.6	
standard deviation	± 6.97	± 8.5	
Gender categorical Units: Subjects			
Male	27	24	

ECOG scale of Performance Status			
The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis Grade: 0 – Asymptomatic. Fully active. 1 – Symptomatic, but completely ambulatory. 2 – Symptomatic, <50% in bed during the day. 3 – Symptomatic, >50% in bed, but not bedbound. 4 – Bed bound. Completely disabled. ECOG=Eastern Cooperative Oncology Group			
Units: Subjects			
Grade 0	22	18	
Grade 1	5	5	
Grade 2		1	
Grade 3			
Grade 4			
Body Mass Index (BMI) Units: (kg/m2			
arithmetic mean	26.99	26.86	
standard deviation	± 3.56	± 3.34	

End points

End points reporting groups

Reporting group title	Zoreline (Test product)
Reporting group description: -	
Reporting group title	Zoladex (Reference product)
Reporting group description: -	
Subject analysis set title	Zoreline (Test product) - PP set
Subject analysis set type	Per protocol

Subject analysis set description:

Included all subjects who received Zoreline (Test product), had at least 1 post-dose assessment, and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin plasma concentrations. These included, but are not limited to, predefined not allowed concomitant medications and delayed visit schedules.

Subject analysis set title	Zoladex (Reference product) - PP set
Subject analysis set type	Per protocol

Subject analysis set description:

Included all subjects who received Zoladex (Reference product), had at least 1 post-dose assessment, and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin plasma concentrations. These included, but are not limited to, predefined not allowed concomitant medications and delayed visit schedules.

Primary: 1_PK -- Cmax -- Maximum measured goserelin plasma concentration

End point title	1_PK -- Cmax -- Maximum measured goserelin plasma concentration

End point description:

Cmax: Maximum measured goserelin plasma concentration.

Ultra-performance liquid chromatography method with triple quadrupole tandem mass spectrometric detection (UPLC-MS/MS) was used for the quantification of goserelin in human plasma.

For all pharmacokinetic (PK) parameters, the results are presented for the per protocol (PP) population.

The PP included all patients of the intention-to-treat (ITT) population who completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin plasma concentrations. These included, but are not limited to, predefined not allowed concomitant medications and delayed visit schedules. Patients were analysed based on the treatment that they actually received.

The intent-to-treat (ITT) population was composed of all subjects who received study drug and had at least 1 post-dose assessment.

End point type	Primary

End point timeframe:

Blood sampling for evaluation of PK parameters of goserelin was performed:

Day 1 -30 min (Baseline), and after implant injection on Day 1 at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h; and on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h)

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[1]	24[2]		
Units: µg/L				
arithmetic mean (standard deviation)	18.826 (± 7.9783)	7.951 (± 2.6393)		

Notes:

[1] - Per Protocol Population

[2] - Per Protocol Population

Statistical analyses

Statistical analysis title	1_Cmax

Statistical analysis description:

ANCOVA was performed on log-transformed PK parameters AUC0-t, AUC0-tcom, and Cmax. The ANCOVA model included the treatment and body weight as fixed effects. From each ANCOVA, the geometric least square means (GLSM) adjusted for body weight with its 95% CI were computed for each treatment, by taking the anti-log of the least square means (LSM) adjusted for body weight and its 95% CI provided by the model.

Ratio of GLSM (test product vs reference product) and its 90% CI are presented.

Comparison groups	Zoreline (Test product) v Zoladex (Reference product)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other[3]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	2.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.91
upper limit	2.81

Notes:

[3] - The study in male patient with prostate cancer does not aim to demonstrate the PK bioequivalence, but to further support the safety comparison between of Zoreline 10.8 mg and Zoladex® LA 10.8 mg, as part of regulatory documentation.

Primary: 2_PK -- AUC(0-t) -- Area under the goserelin plasma concentration curve -- To the last measurable concentration

End point title	2_PK -- AUC(0-t) -- Area under the goserelin plasma concentration curve -- To the last measurable concentration

End point description:

AUC(0-t): Area under the goserelin plasma concentration curve from administration to the last measurable concentration at time t in both groups.

End point type	Primary

End point timeframe:

Blood sampling for evaluation of PK parameters of goserelin was performed:

Day 1 -30 min (Baseline), and after implant injection on Day 1 at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h; and on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h)

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[4]	24[5]		
Units: µg.h/L				
arithmetic mean (standard deviation)	904.400 (± 350.9048)	954.980 (± 322.8665)		

Notes:

[4] - Per Protocol Population

[5] - Per Protocol Population

Statistical analyses

Statistical analysis title	AUC(0-t)

Statistical analysis description:

Please see description for statistical analysis in end point 1.

Comparison groups	Zoreline (Test product) v Zoladex (Reference product)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other[6]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.12

Notes:

[6] - This study in male patient with prostate cancer does not aim to demonstrate the PK bioequivalence, but to further support the safety comparison between of Zoreline 10.8 mg and Zoladex® LA 10.8 mg, as part of regulatory documentation.

Primary: 3_PK -- AUC(0-tcom) -- Area under the goserelin plasma concentration curve -- Last common measurable time-point for all patients in both groups

End point title	3_PK -- AUC(0-tcom) -- Area under the goserelin plasma concentration curve -- Last common measurable time-point for all patients in both groups

End point description:

AUC(0-tcom): Area under the goserelin plasma concentration curve from administration to the last common measurable time-point within all patients in both groups.

End point type	Primary

End point timeframe:

Blood sampling for evaluation of PK parameters of goserelin was performed:

Day 1 -30 min (Baseline), and after implant injection on Day 1 at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h; and on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h)

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[7]	24[8]		
Units: µg.h/L				
arithmetic mean (standard deviation)	904.400 (± 350.9048)	954.980 (± 322.8665)		

Notes:

[7] - Per Protocol Population

[8] - Per Protocol Population

Statistical analyses

Statistical analysis title	AUC(0-tcom)

Statistical analysis description:

Please see description for statistical analysis in end point 1.

Comparison groups	Zoladex (Reference product) v Zoreline (Test product)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other[9]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.12

Notes:

[9] - This study in male patient with prostate cancer does not aim to demonstrate the PK bioequivalence, but to further support the safety comparison between of Zoreline 10.8 mg and Zoladex® LA 10.8 mg, as part of regulatory documentation

Secondary: 4_PK -- tmax -- Time until the maximum measured goserelin plasma concentration

End point title	4_PK -- tmax -- Time until the maximum measured goserelin plasma concentration

End point description:

tmax: Time until the maximum measured goserelin plasma concentration is reached.

End point type	Secondary

End point timeframe:

Blood sampling for evaluation of PK parameters of goserelin was performed:

Day 1 -30 min (Baseline), and after implant injection on Day 1 at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h; and on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h)

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[10]	24[11]		
Units: hour				
median (full range (min-max))	2.50 (1.42 to 8.00)	4.00 (1.45 to 12.00)		

Notes:

[10] - Per Protocol Population

[11] - Per Protocol Population

Statistical analyses

No statistical analyses for this end point

Secondary: 5_PK -- C(Day85) -- Goserelin plasma concentration -- At the end of the treatment

End point title	5_PK -- C(Day85) -- Goserelin plasma concentration -- At the end of the treatment

End point description:

C(day85): Goserelin plasma concentration at the end of the treatment period.

End point type	Secondary

End point timeframe:

Blood sampling for evaluation of PK parameters of goserelin was performed:

Day 1 -30 min (Baseline), and after implant injection on Day 1 at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h; and on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h)

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[12]	24[13]		
Units: µg/L				
arithmetic mean (standard deviation)	0.105 (± 0.0928)	0.161 (± 0.1030)		

Notes:

[12] - Per Protocol Population

[13] - Per Protocol Population

Statistical analyses

No statistical analyses for this end point

Secondary: 6_PK -- Cmin -- Minimum post-dose goserelin plasma concentration

End point title	6_PK -- Cmin -- Minimum post-dose goserelin plasma concentration

End point description:

Cmin: Minimum post-dose goserelin plasma concentration.

End point type	Secondary

End point timeframe:

Blood sampling for evaluation of PK parameters of goserelin was performed:

Day 1 -30 min (Baseline), and after implant injection on Day 1 at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 h; and on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h)

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[14]	24[15]		
Units: µg/L				
arithmetic mean (standard deviation)	0.043 (± 0.0345)	0.102 (± 0.0647)		

Notes:

[14] - Per Protocol Population

[15] - Per Protocol Population

Statistical analyses

No statistical analyses for this end point

Secondary: 7_PD -- Cmax -- Plasma Testosterone

End point title	7_PD -- Cmax -- Plasma Testosterone

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.

Total testosterone was measured in plasma, using ultra-performance liquid chromatography method with triple quadrupole tandem mass spectrometric detection (UPLC-MS/MS).

For all pharmacodynamic (PD) parameters, the results are presented for the per protocol (PP) population.

End point type	Secondary

End point timeframe:

Blood sampling for evaluation of PD parameters of testosterone was performed at:

Day 1 -30 min (Baseline), and after implant injection on Day 1 after 12 h; on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h interval).

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[16]	24[17]		
Units: µg/L				
arithmetic mean (standard deviation)	7.839 (± 2.4317)	7.063 (± 2.5346)		

Notes:

[16] - Per Protocol Population

[17] - Per Protocol Population

Statistical analyses

No statistical analyses for this end point

Secondary: 8_PD -- Cmin -- Plasma Testosterone

End point title	8_PD -- Cmin -- Plasma Testosterone

End point description:

Cmin -- Plasma Testosterone -- Minimum measured testosterone plasma concentration.

For further information, please see the description in end point 7.

End point type	Secondary

End point timeframe:

Blood sampling for evaluation of PD parameters of testosterone was performed at:

Day 1 -30 min (Baseline), and after implant injection on Day 1 after 12 h; on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h interval).

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[18]	24[19]		
Units: µg/L				
arithmetic mean (standard deviation)	0.112 (± 0.0856)	0.095 (± 0.0534)		

Notes:

[18] - Per Protocol Population

[19] - Per Protocol Population

Statistical analyses

No statistical analyses for this end point

Secondary: 9_PD -- AUC(0-t) -- Testosterone

End point title	9_PD -- AUC(0-t) -- Testosterone

End point description:

AUC(0-t) -- Testosterone -- Area under the testosterone plasma concentration curve from administration to the last measurable concentration at time t in both groups.

For further information, please see the description in end point 7.

End point type	Secondary

End point timeframe:

Blood sampling for evaluation of PD parameters of testosterone was performed at:

Day 1 -30 min (Baseline), and after implant injection on Day 1 after 12 h; on Day 2, 3, 4, 8, 15, 22, 29, 36, 43, 50, 57, 71, 78, 85 (per 24h interval).

End point values	Zoreline (Test product)	Zoladex (Reference product)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[20]	24[21]		
Units: µg.h/L				
arithmetic mean (standard deviation)	2411.927 (± 1348.5835)	1739.898 (± 516.1524)		

Notes:

[20] - Per Protocol Population

[21] - Per Protocol Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events 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).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Zoreline (Test)
Reporting group description: -	
Reporting group title	Zoladex (Reference)

Reporting group description: -

Serious adverse events	Zoreline (Test)	Zoladex (Reference)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
ischemic stroke			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Zoreline (Test)	Zoladex (Reference)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 29 (62.07%)	12 / 29 (41.38%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 29 (27.59%)	5 / 29 (17.24%)	
occurrences (all)	8	5	
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 29 (10.34%)	2 / 29 (6.90%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 29 (10.34%)	0 / 29 (0.00%)	
occurrences (all)	4	0	
Haematuria			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported