



## 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<br>, Novalon S.A., +32 43492822, Clinical.Trials@mithra.com |
| Scientific contact           | Clinical Study Leader<br>, 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:

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## Results analysis stage

|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 02 May 2017 |
| Is this the analysis of the primary completion data? | No          |
| <hr/>                                                |             |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 03 May 2016 |
| Was the trial ended prematurely?                     | No          |

Notes:

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## 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 ( $\leq 50$  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;

C<sub>max</sub>=Maximum measured plasma concentration;

C<sub>min</sub>=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  $\leq 2$  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).

| <b>Number of subjects in period 1</b> | Treatment<br>(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/m <sup>2</sup>                                                                                   |           |       |  |
| 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<br>Units: years<br>arithmetic mean<br>standard deviation                    | 74.2<br>± 6.47 |  |  |
| Gender categorical<br>Units: Subjects                                                      |                |  |  |
| Female                                                                                     | 0              |  |  |
| Male                                                                                       | 125            |  |  |
| Race<br>Units: Subjects                                                                    |                |  |  |
| Caucasian                                                                                  | 125            |  |  |
| Body mass index (BMI)<br>Units: kg/m <sup>2</sup><br>arithmetic mean<br>standard deviation | 27.56<br>±     |  |  |

## 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 <sup>[2]</sup>   |  |  |  |
| 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 -- $\leq 50$ ng/dL (mITT set)

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | 1b_Testosterone suppression in plasma -- $\leq 50$ ng/dL (mITT set) <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------------------------|

End point description:

Testosterone suppression in plasma to  $\leq 50$  ng/dL

A responder was defined as a subject who reached plasma testosterone levels below the castrate level ( $\leq 50$  ng/dL) by Day 29 of Cycle 1 at the latest and maintained plasma testosterone levels below the castrate level ( $\leq 50$  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  $\geq 90\%$ .

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 <sup>[4]</sup>   |  |  |  |
| 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 <sup>[5]</sup>   |  |  |  |
| 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 <sup>[6]</sup>   |  |  |  |
| Units: day.ng/dL                     |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| AUC 85d (Cycle 1)                    | 9153 (± 3980)        |  |  |  |
| AUC 85d (Cycle 2)                    | 1638 (± 1695)        |  |  |  |
| AUC (0-t)                            | 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  $\geq 2$ -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 <sup>[7]</sup>   |  |  |  |
| 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 ( $\leq 50$  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) |           |

|                                      |                      |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| <b>End point values</b>              | Treatment (Zoreline) |  |  |  |
| Subject group type                   | Reporting group      |  |  |  |
| Number of subjects analysed          | 141 <sup>[8]</sup>   |  |  |  |
| 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) |           |

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Treatment (Zoreline) |  |  |  |
| Subject group type          | Reporting group      |  |  |  |
| Number of subjects analysed | 102 <sup>[9]</sup>   |  |  |  |
| 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 <sup>[10]</sup>  |  |  |  |
| 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 <sup>[11]</sup>  |  |  |  |
| 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 <sup>[12]</sup>  |  |  |  |
| 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 <sup>[13]</sup>  |  |  |  |
| 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 <sup>[14]</sup>  |  |  |  |
| Units: day.pg/mL                     |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| Cycle 1                              | 32148 (± 11146)      |  |  |  |
| Cycle 2                              | 40046 (± 13818)      |  |  |  |

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Notes:

[14] - ITT Population

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### **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 %

| <b>Non-serious adverse events</b>                     | Treatment<br>(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: <ul style="list-style-type: none"><li>• 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.</li></ul>                                                                                                                                                                                                                                                       |
| 06 May 2015     | On 06-May-2015, a second substantial amendment was made to the original protocol included: <ul style="list-style-type: none"><li>• Inclusion criterion 7 was changed from "PSA level <math>\geq</math> 4 ng/mL" to "PSA level <math>\geq</math> 4 ng/mL; Exception: for patients who have had previous prostatectomy and/or prostate radiotherapy, all PSA levels are allowed."</li><li>• Inclusion criterion 9 was changed. Patients enrolled into the study had to have BMI ranging between 18.5 and 35 kg/m<sup>2</sup> (inclusive) instead of 18.5 and 32 kg/m<sup>2</sup> (inclusive).</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported