



Clinical trial results:

Open-label, multi-center, randomized parallel group study to assess the pharmacokinetic (PK) profile of Zoreline 3.6 mg goserelin subcutaneous implant (test product, Novalon S.A.) and of Zoladex® 3.6 mg goserelin subcutaneous implant (reference product, AstraZeneca UK Limited), in women with confirmed endometriosis

Summary

EudraCT number	2015-005124-25
Trial protocol	BG
Global end of trial date	26 October 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	No0001-C201
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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	10 July 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Characterize the goserelin plasma concentration pharmacokinetic profile from Day 1 to 29 of Period 1 and Day 1 (coinciding with Day 29 of Period 1) to Day 17 of Period 2 (2 treatment cycles whereas Day 29 of Period 2 represents the end of treatment), after injection with Zoreline 3.6 mg or Zoladex® 3.6 mg subcutaneous implant in female subjects with confirmed endometriosis. The study was required for a marketing authorization application.

Zoreline was developed as a generic version of Zoladex® 3.6 mg goserelin SC implant (AstraZeneca, UK). The active pharmaceutical ingredient and excipients in Zoreline and Zoladex® are identical.

Goserelin is a type of hormone therapy called luteinising hormone blocker. Goserelin stops the release of luteinising hormone (LH) from the pituitary gland and follicle stimulating hormone (FSH) secretion leading to a fall in serum estradiol concentrations. High levels of estradiol can affect uterine tissue and trigger endometriosis.

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 in all trial related documents.

Background therapy:

Not applicable.

Please note:

The trial was originally designed to investigate pharmacokinetic (PK) parameters after a single injection of the study products (i.e., one Treatment Period). In an amendment to the protocol during the trial, a second Treatment Period was added to provide further data and improve comparability with the reference product.

The study consisted of one (Cohort 1; before protocol amendment) or two (Cohort 2; after protocol amendment) consecutive 28-day Treatment Periods. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1. An End of Study visit was performed on Day 29 of Treatment Period 1 for Cohort 1 and on Day 29 of Treatment Period 2 for Cohort 2.

Results of the study are presented separately for the two cohorts, whenever relevant.

Evidence for comparator:

Not applicable

LIST OF ABBREVIATIONS USED IN THIS STUDY ENTRY

AE=Adverse event;

ANCOVA=Analysis of covariance;

AUC(0-t)=Area under the plasma concentration-time curve, calculated to the last quantifiable data point;

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

Cmax=Maximum measured plasma concentration;
 Cmin=Minimum post-dose plasma concentration;
 GLSM=Geometric least square mean;
 LC-MS/MS=Liquid chromatography with tandem mass spectrometry;
 LH=Luteinizing hormone;
 LHRH=Luteinizing hormone releasing hormone;
 PD=Pharmacodynamic;
 PK=Pharmacokinetic;
 PP=Per Protocol. The Per Protocol population included all patients who completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin or estradiol plasma concentrations. These included but were not limited to predefined disallowed concomitant medications and delayed visit schedules.
 TEAEs=treatment-emergent adverse events;
 Tmax=Time until the maximum measured plasma concentration

Actual start date of recruitment	26 September 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	Bulgaria: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	68
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female adult subjects (age between 18 and 45 years inclusive, white /Caucasian) with confirmed endometriosis were screened according to the study inclusion and exclusion criteria. Overall, 68 subjects were randomized (N=34 subjects in the test treatment group and N=34 subjects in the reference group).

Pre-assignment

Screening details:

At the screening visit (up to 14 days before first study treatment administration), 68 subjects meeting all the eligibility criteria were randomized 1:1 to receive either the test or reference product.

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	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study. Blinding was only applied to laboratory staff performing the bioanalysis (i.e., they were not provided with the randomization codes).

Arms

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

Arm description:

Test product was administered either once (Cohort 1, before protocol amendment) or twice (Cohort 2; after protocol amendment), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

The maximum study duration was approximately 43 days for Cohort 1 (one injection) and 71 days for Cohort 2 (two injections), including the screening period.

Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Arm type	Experimental
Investigational medicinal product name	Zoreline
Investigational medicinal product code	
Other name	Test product
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

Test product name : Zoreline (Test product)

Formulation : Goserelin acetate

Strength of dosage form : 3.6 mg subcutaneous implant

Zoreline 3.6 mg subcutaneous implant was formulated as a sterile implant, in a pre-filled, single-use, disposable syringe device.

Test product was administered either once (Cohort 1) or twice (Cohort 2), on Day 1 of each 28-day treatment period.

Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

Test product was administered subcutaneously 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 anesthetic was allowed if this was part of local practice.

Arm title	Zoladex (Reference product)
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Arm description:

Reference product was administered either once (Cohort 1; before protocol amendment) or twice (Cohort 2; after protocol amendment), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

The maximum study duration was approximately 43 days for Cohort 1 (one injection) and 71 days for Cohort 2 (two injections), including the screening period.

Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

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

Dosage and administration details:

Reference product name : Zoladex®

Formulation : Goserelin acetate

Strength of dosage form : 3.6 mg subcutaneous implant,

Marketing Authorization Holder : AstraZeneca UK Limited

Zoladex® 3.6 mg subcutaneous implant was supplied as a sterile implant, in a pre-filled disposable syringe device.

Reference product was administered either once (Cohort 1) or twice (Cohort 2), on Day 1 of each 28-day treatment period.

Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

Reference product was administered subcutaneously 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 anesthetic was allowed if this was part of local practice.

Number of subjects in period 1	Zoreline (Test product)	Zoladex (Reference product)
Started	34	34
Completed	31	30
Not completed	3	4
Consent withdrawn by subject	3	4

Baseline characteristics

Reporting groups

Reporting group title	Zoreline (Test product)
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Reporting group description:

Test product was administered either once (Cohort 1, before protocol amendment) or twice (Cohort 2; after protocol amendment), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

The maximum study duration was approximately 43 days for Cohort 1 (one injection) and 71 days for Cohort 2 (two injections), including the screening period.

Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Reporting group title	Zoladex (Reference product)
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Reporting group description:

Reference product was administered either once (Cohort 1; before protocol amendment) or twice (Cohort 2; after protocol amendment), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

The maximum study duration was approximately 43 days for Cohort 1 (one injection) and 71 days for Cohort 2 (two injections), including the screening period.

Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Reporting group values	Zoreline (Test product)	Zoladex (Reference product)	Total
Number of subjects	34	34	68
Age categorical			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: Subjects			
Adults (18-64 years)	34	34	68
Age continuous			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: years			
arithmetic mean	31.83	30.97	
standard deviation	± 4.94	± 5.79	-
Gender categorical			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: Subjects			
Female	34	34	68
Male	0	0	0
Race			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			

Units: Subjects			
White/Caucasian	34	34	68

Body mass index (BMI)			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: kg/m ²			
arithmetic mean	25.06	24.49	
standard deviation	± 3.88	± 3.54	-

Subject analysis sets

Subject analysis set title	Cohort 1 - Test product
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohort 1: Patients receiving one treatment period of Test product (recruited before protocol amendment)	
Subject analysis set title	Cohort 2 - Test product
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohort 2: Patients receiving two treatment periods of Test product (recruited after protocol amendment)	
Subject analysis set title	Cohort 1 - Reference product
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohort 1: Patients receiving one treatment period of Reference product (recruited before protocol amendment)	
Subject analysis set title	Cohort 2 - Reference product
Subject analysis set type	Safety analysis
Subject analysis set description:	
Cohort 2: Patients receiving two treatment periods of Reference product (recruited after protocol amendment)	
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), and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin or estradiol plasma concentrations. These included but were not limited to predefined disallowed 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), and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin or estradiol plasma concentrations. These included but were not limited to predefined disallowed concomitant medications and delayed visit schedules.	

Reporting group values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product
Number of subjects	24	10	24
Age categorical			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			

Units: Subjects			
Adults (18-64 years)	24	10	24

Age continuous			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: years			
arithmetic mean	31.38	32.90	31.04
standard deviation	± 4.64	± 5.72	± 5.61
Gender categorical			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: Subjects			
Female	24	10	24
Male	0	0	0
Race			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: Subjects			
White/Caucasian	24	10	24
Body mass index (BMI)			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: kg/m ²			
arithmetic mean	25.26	24.57	24.35
standard deviation	± 4.02	± 3.69	± 3.42

Reporting group values	Cohort 2 - Reference product	Zoreline (Test product) - PP set	Zoladex (Reference product) - PP set
Number of subjects	10	29	29
Age categorical			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: Subjects			
Adults (18-64 years)	10	29	29
Age continuous			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: years			
arithmetic mean	30.80	31.76	31.07
standard deviation	± 6.51	± 5.05	± 5.54
Gender categorical			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment) Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			

Safety Population			
Units: Subjects			
Female	10	29	29
Male	0		
Race			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment)			
Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: Subjects			
White/Caucasian	10	29	29
Body mass index (BMI)			
Cohort 1: Patients receiving one treatment period (recruited before protocol amendment)			
Cohort 2: Patients receiving two treatment periods (recruited after protocol amendment)			
Safety Population			
Units: kg/m ²			
arithmetic mean	24.83	25.09	24.75
standard deviation	± 3.99	± 3.94	± 3.58

End points

End points reporting groups

Reporting group title	Zoreline (Test product)
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Reporting group description:

Test product was administered either once (Cohort 1, before protocol amendment) or twice (Cohort 2; after protocol amendment), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

The maximum study duration was approximately 43 days for Cohort 1 (one injection) and 71 days for Cohort 2 (two injections), including the screening period.

Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Reporting group title	Zoladex (Reference product)
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Reporting group description:

Reference product was administered either once (Cohort 1; before protocol amendment) or twice (Cohort 2; after protocol amendment), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1.

The maximum study duration was approximately 43 days for Cohort 1 (one injection) and 71 days for Cohort 2 (two injections), including the screening period.

Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Subject analysis set title	Cohort 1 - Test product
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Cohort 1: Patients receiving one treatment period of Test product (recruited before protocol amendment)

Subject analysis set title	Cohort 2 - Test product
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Cohort 2: Patients receiving two treatment periods of Test product (recruited after protocol amendment)

Subject analysis set title	Cohort 1 - Reference product
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Cohort 1: Patients receiving one treatment period of Reference product (recruited before protocol amendment)

Subject analysis set title	Cohort 2 - Reference product
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Cohort 2: Patients receiving two treatment periods of Reference product (recruited after protocol amendment)

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

Included all subjects who received Zoreline (Test product), and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin or estradiol plasma concentrations. These included but were not limited to predefined disallowed concomitant medications and delayed visit schedules.

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

Included all subjects who received Zoladex (Reference product), and completed the treatment period, excluding patients with major protocol deviations, i.e. deviations that have major impact on the assessments of goserelin or estradiol plasma concentrations. These included but were not limited to

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

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

Cmax: Maximum measured goserelin plasma concentration.

Plasma concentration of goserelin was measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS).

For pharmacokinetic (PK) parameters, results are presented for the per protocol (PP) population i.e. all patients completing the treatment period, excluding those with major protocol deviations wrt. goserelin or estradiol plasma concentration.

Timeframe

Cohort 1

Pre-dose and at 4h, 8h, and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29.

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22.

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), 4h, 8h,

End point type	Primary
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End point timeframe:

Timeframe for blood sampling, used for the evaluation of PK parameters of goserelin are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[1]	9	22	7
Units: ng/mL				
arithmetic mean (standard deviation)	2.81675 (± 1.162417)	2.41296 (± 0.666803)	2.27258 (± 1.649437)	1.19651 (± 0.471987)

Notes:

[1] - Per Protocol Population was used for all groups analysed.

Statistical analyses

Statistical analysis title	1_Cmax -- Cohort 1
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Statistical analysis description:

Analysis of covariance (ANCOVA) was performed on the log-transformed PK parameters AUC(0-t), AUC(0-tcom), and Cmax, by cohort. The ANCOVA model included the treatment and body weight (assessed at screening visit) as fixed effects.

Comparison groups	Cohort 1 - Reference product v Cohort 1 - Test product
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Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other ^[2]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	1.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.86

Notes:

[2] - From each ANCOVA, the geometric least square means (GLSM) adjusted for body weight with its 95% Confidence Intervals (95%) was 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.

The ratio of GLSM (test product versus reference product) and its 90% CI was calculated by taking the anti-log of the difference of least square means (LSMs).

Statistical analysis title	2_Cmax -- Cohort 2
Statistical analysis description:	
For further details - please see the 'Analysis description' shown for end point 1 - statistical analysis 1.	
Comparison groups	Cohort 2 - Test product v Cohort 2 - Reference product
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other ^[3]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	2.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.5
upper limit	2.89

Notes:

[3] - For further details - please see the field 'Analysis type comment' shown for end point 1 - statistical analysis 1.

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
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End point description:

PK -- AUC (0-t) -- Area under the goserelin plasma concentration curve -- To the last measurable concentration

Timeframe

Cohort 1

Pre-dose and at 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29.

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22.

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), 4h, 8h and 12h

post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Primary
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End point timeframe:

Timeframe for blood sampling, used for the evaluation of PK parameters of goserelin are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[4]	9	22	7
Units: ng.h/mL				
arithmetic mean (standard deviation)	331.865 (± 167.2125)	218.192 (± 27.6298)	319.167 (± 160.1637)	157.915 (± 38.2840)

Notes:

[4] - Per Protocol Population was used for all groups analysed.

Statistical analyses

Statistical analysis title	1_AUC (0-t) -- Cohort 1
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Statistical analysis description:

For further details - please see the 'Analysis description' shown for end point 1 - statistical analysis 1.

Comparison groups	Cohort 1 - Test product v Cohort 1 - Reference product
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other ^[5]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	0.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.68
upper limit	1.31

Notes:

[5] - For further details - please see the field 'Analysis type comment' shown for end point 1 - statistical analysis 1.

Statistical analysis title	2_AUC (0-t) -- Cohort 2
Comparison groups	Cohort 2 - Test product v Cohort 2 - Reference product
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	1.4

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.15
upper limit	1.7

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

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

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

Timeframe

Cohort 1

Pre-dose and at 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29.

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22.

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Primary
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End point timeframe:

Timeframe for blood sampling, used for the evaluation of PK parameters of goserelin are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[6]	9	22	7
Units: ng.h/mL				
arithmetic mean (standard deviation)	290.674 (± 149.6395)	218.192 (± 27.6298)	261.173 (± 134.6129)	157.915 (± 38.2840)

Notes:

[6] - Per Protocol Population was used for all groups analysed.

Statistical analyses

Statistical analysis title	1_AUC (0-tcom) -- Cohort 1
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Statistical analysis description:

For further details - please see the 'Analysis description' shown for end point 1 - statistical analysis 1.

Comparison groups	Cohort 1 - Test product v Cohort 1 - Reference product
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Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other ^[7]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.72
upper limit	1.41

Notes:

[7] - For further details - please see the field 'Analysis type comment' shown for end point 1 - statistical analysis 1.

Statistical analysis title	2_AUC (0-tcom) -- Cohort 2
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Statistical analysis description:

For further details - please see the 'Analysis description' shown for end point 1 - statistical analysis 1.

Comparison groups	Cohort 2 - Test product v Cohort 2 - Reference product
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other ^[8]
Method	ANCOVA
Parameter estimate	Ratio of GLSM
Point estimate	1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.15
upper limit	1.7

Notes:

[8] - For further details - please see the field 'Analysis type comment' shown for end point 1 - statistical analysis 1.

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
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End point description:

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

Timeframe:

Cohort 1

Pre-dose and at 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Secondary
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End point timeframe:

Timeframe for blood sampling used for the evaluation of PK parameters of goserelin are shown for

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[9]	9	22	7
Units: hour				
median (full range (min-max))	4.00 (4.00 to 8.00)	4.00 (4.00 to 8.00)	311.88 (4.00 to 407.37)	313.10 (287.35 to 383.87)

Notes:

[9] - Per Protocol Population was used for all groups analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: 5_PK -- C(Day29, Period 1) -- Goserelin plasma concentration -- At the end of the treatment

End point title	5_PK -- C(Day29, Period 1) -- Goserelin plasma concentration - - At the end of the treatment
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End point description:

CDay29 of Period 1 -- Goserelin plasma concentration at the end of the first dosing interval

Cohort 1

Pre-dose and at 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Secondary
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End point timeframe:

Timeframe for blood sampling used for the evaluation of PK parameters of goserelin are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[10]	9	22	7
Units: ng/mL				
arithmetic mean (standard deviation)				
CDay29 of Period 1	0.12421 (± 0.072045)	0.14726 (± 0.091587)	0.22813 (± 0.120940)	0.17374 (± 0.054663)

Notes:

[10] - Per Protocol Population was used for all groups analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: 6_PK -- C(Day17 of Period 2) -- Goserelin plasma concentration -- At the end of the treatment

End point title	6_PK -- C(Day17 of Period 2) -- Goserelin plasma concentration -- At the end of the treatment
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End point description:

CDay17 of Period 2 -- Goserelin plasma concentration at the end of the 17 days post second implant injection.

Cohort 1

Pre-dose and at 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), 4h, 8h and 12h post-dose (Day 1), at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Secondary
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End point timeframe:

Timeframe for blood sampling used for the evaluation of PK parameters of goserelin are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 2 - Test product	Cohort 2 - Reference product		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 ^[11]	7		
Units: ng/mL				
arithmetic mean (standard deviation)				
CDay17 of Period 2	0.38084 (± 0.095024)	0.63150 (± 0.194419)		

Notes:

[11] - Per Protocol Population was used for all groups analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: 7_PD -- Cmax -- Plasma estradiol

End point title	7_PD -- Cmax -- Plasma estradiol
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End point description:

PD -- Cmax -- Plasma estradiol

Plasma concentration of estradiol was measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Timeframe:

Cohort 1

Pre-dose and at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), and at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Secondary
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End point timeframe:

Timeframe for blood sampling used for the evaluation of PD parameters of estradiol are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[12]	9	22	7
Units: ng/mL				
arithmetic mean (standard deviation)	0.23977 (± 0.131051)	0.00625 (± 0.005407)	0.32211 (± 0.387875)	0.01499 (± 0.016481)

Notes:

[12] - Per Protocol Population was used for all groups analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: 8_PD -- Cmin -- Plasma estradiol

End point title	8_PD -- Cmin -- Plasma estradiol
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End point description:

PD -- Cmin -- Plasma estradiol

Timeframe:

Cohort 1

Pre-dose and at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), and at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Secondary
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End point timeframe:

Timeframe for blood sampling used for the evaluation of PD parameters of estradiol are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[13]	9	22	7
Units: ng/mL				
median (full range (min-max))	0.0026 (0.0026 to 0.0077)	0.0026 (0.0026 to 0.0064)	0.0026 (0.0026 to 0.0074)	0.0026 (0.0026 to 0.0026)

Notes:

[13] - Per Protocol Population was used for all groups analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: 9_PD -- AUC (0-t) -- Plasma estradiol

End point title	9_PD -- AUC (0-t) -- Plasma estradiol
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End point description:

PD -- AUC (0-t) -- Plasma estradiol

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

Timeframe:

Cohort 1

Pre-dose and at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Day 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 22, and 29

Cohort 2

Treatment Period 1: Pre-dose (Day 1) and then on Days 11, 13, 14, 15, 16, 18, 19, and 22

Treatment Period 2: Pre-dose (Day 1 coinciding with Day 29 of Treatment Period 1), and at 24h (Day 2), 48h (Day 3), and 72h (Day 4), and at Days 6, 8, 9, 11, 12, 13, 14, 15, and 17.

End point type	Secondary
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End point timeframe:

Timeframe for blood sampling used for the evaluation of PD parameters of estradiol are shown for Cohort 1 and Cohort 2 in the field -- 'End point description'.

End point values	Cohort 1 - Test product	Cohort 2 - Test product	Cohort 1 - Reference product	Cohort 2 - Reference product
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20 ^[14]	9	22	7
Units: ng.h/mL				
arithmetic mean (standard deviation)	33.799 ($\pm$ 30.6097)	0.791 ($\pm$ 1.2864)	54.462 ($\pm$ 67.6323)	1.626 ($\pm$ 1.5389)

Notes:

[14] - Per Protocol Population was used for all groups analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) 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).

The safety population was used for the analysis of AEs.

Safety population included all subjects who were randomized and received study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Zoreline (Test)
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Reporting group description:

Test product was administered either once (Cohort 1) or twice (Cohort 2), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1. Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Reporting group title	Zoladex (Reference)
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Reporting group description:

Reference product was administered either once (Cohort 1) or twice (Cohort 2), on Day 1 of each 28-day treatment period. Day 1 of Treatment Period 2 coincided with Day 29 of Treatment Period 1. Test product was administered subcutaneously into the anterior abdominal wall below the navel line using an aseptic technique by a trained member of the clinical team.

Serious adverse events	Zoreline (Test)	Zoladex (Reference)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)	0 / 34 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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	9 / 34 (26.47%)	7 / 34 (20.59%)	
Investigations			

Weight increased subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 34 (0.00%) 0	
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	3 / 34 (8.82%) 3	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 5 1 / 34 (2.94%) 1	3 / 34 (8.82%) 4 0 / 34 (0.00%) 0	
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) Discomfort subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1 0 / 34 (0.00%) 0	1 / 34 (2.94%) 1 0 / 34 (0.00%) 0 0 / 34 (0.00%) 0 1 / 34 (2.94%) 1	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting	1 / 34 (2.94%) 1 0 / 34 (0.00%) 0	0 / 34 (0.00%) 0 1 / 34 (2.94%) 1	

subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 34 (2.94%) 1	
Reproductive system and breast disorders			
Breast swelling			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Oligomenorrhoea			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2017	An amendment was issued on 25 May 2017 to add a second period of treatment to improve PK and PD profile comparability with the reference product. A second dose of treatment was therefore scheduled at Day 29 of the first treatment period. The protocol amendment also involved a change to the blood sampling schedule for Treatment Period 1 and new sampling time points for Treatment Period 2. Patients recruited before and after protocol amendment were referred to as Cohort 1 and Cohort 2, respectively.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.

Notes: