



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 subjects with prostate cancer.

Summary

EudraCT number	2019-000593-32
Trial protocol	DE
Global end of trial date	06 April 2020

Results information

Result version number	v1 (current)
This version publication date	16 May 2021
First version publication date	16 May 2021
Summary attachment (see zip file)	Synopsis CSR (SMS-0480_NOVALON_Zoreline CSR_Final_Synopsis_01Apr2021.pdf)

Trial information

Trial identification

Sponsor protocol code	MIT-Zo002-C301
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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, Liege, Belgium, 4000
Public contact	Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals, Novalon S.A, +32 43492822, clinicaltrials@mithra.com
Scientific contact	Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals, Novalon S.A, +32 43492822, clinicaltrials@mithra.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the ability of Zoreline 10.8 mg subcutaneous implant to induce testosterone serum suppression (≤ 50 ng/dL) in male subjects with prostate cancer by Day 29 of Cycle 1 at the latest and have this confirmed at Day 85 of Cycle 1 and Day 85 of Cycle 2 (End of Treatment)

Protection of trial subjects:

Subjects had to abstain from the use of all concomitant medications as described in the exclusion criteria: GnRH agonist or antagonist therapy, and any treatment that interferes with testosterone serum level. Previous and concomitant treatment with GnRH analogs was not allowed. However, subjects who previously underwent an intermittent treatment scheme could be included if no more than two treatment cycles were received and if the last treatment injection was not within 6 months of the screening visit (as per eligibility criteria). A treatment cycle was defined as the continuous and repeated administration of a GnRH analog (according to the prescribing information) until discontinuation of treatment based on the subject's physical and / or disease status as judged by the Investigator. Non-steroidal anti-androgens (such as bicalutamide, flutamide, nilutamide, enzalutamide) were allowed to prevent disease flare-ups only, caused by testosterone surges. Treatment with non-steroidal anti-androgens was at the discretion of the Investigator. Further occurrence of disease flare-ups caused by testosterone surges had to be treated symptomatically as determined by the Investigator. The following rules had to be taken into account when prescribing other treatments during the subject's participation in the trial:

- Ancillary treatments were allowed to be given as medically indicated; they should have been recorded in the subjects' medical chart and on the appropriate electronic Case Report Form (eCRF);
 - Radiotherapy was allowed to be given concomitantly for control of bone pain or other reasons;
 - Subjects were not allowed to receive other anticancer treatments or other investigational agents from start of trial treatment until the End of Treatment visit;
 - In case of doubt, concomitant medication could be discussed with the Medical Monitor.
- The use of local anesthetic was allowed if this was part of local practice

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2019
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	Moldova, Republic of: 40
Country: Number of subjects enrolled	Georgia: 13
Country: Number of subjects enrolled	Ukraine: 31
Country: Number of subjects enrolled	Germany: 58
Worldwide total number of subjects	142
EEA total number of subjects	58

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	105
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

In 14 trial sites in Germany, Moldova, Georgia and Ukraine, the trial subjects were recruited. In total 142 subjects meeting all eligibility criteria were enrolled. The first patient was included on 14Jun2019. Last study visit before database lock was 06Apr2020.

Pre-assignment

Screening details:

Male subjects (>18 years old) with prostate cancer. 169 subjects were screened and signed the ICF with 142 meeting all eligibility criteria and starting treatment with Zoreline. A total of 24 subjects were part of the pharmacokinetic sub-study. Each enrolled subject received the 10.8 mg goserelin (Zoreline) SC implant

Period 1

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

Arms

Arm title	Each enrolled subject received 10.8 mg Zoreline SC implant
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Arm description:

142 subjects started the treatment with Zoreline. The subjects had to come to the clinic center on Days 1, 2, 4, 8, 15, 29, 30, 36, 57, 84, and on Day 85 of Cycle 1 (=pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57, 84, and on Day 85 of Cycle 2 (which is the End of Treatment day).

A total of 24 subjects were part of the pharmacokinetic (PK) substudy. This group had additional blood samples taken to assess the PK profile of the trial medication in addition to their blood collected for pharmacodynamic and safety assessments. Subjects in the PK substudy had seven additional visits on Days 22, 43, 45, 50, 64, 71 and 78 of Cycle 1. After all the PK substudy was not performed: the study was terminated early because of efficacy risks and the PK parameters were not evaluated because no PK analysis was performed on the respective samples.

Each treatment cycle had a duration of 84 days. The total treatment duration of this trial was 168 days, two cycles.

Arm type	Experimental
Investigational medicinal product name	Zoreline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

10.8 mg depot of Zoreline was injected subcutaneously into the anterior abdominal wall, every 84 days (12 weeks) on Day 1 of Cycle 1 and Day 1 of Cycle 2 (corresponding to Day 85 of Cycle 1).

Number of subjects in period 1	Each enrolled subject received 10.8 mg Zoreline SC implant
Started	142
Completed	31
Not completed	111
Trial termination by sponsor	110

Non-compliance with trial schedule	1
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Baseline characteristics

Reporting groups

Reporting group title	Overall trial
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Reporting group description:

Overall, 169 subjects were screened and signed the ICF to participate in the trial (defined in this trial as the ENR population). Of these, 142 subjects were confirmed eligible on Cycle 1 Day 1, were enrolled in the trial and received at least one dose of trial medication (SAF population). The remainder of 27 subjects did not meet all eligibility criteria and were considered screen failures.

ITT population was identical to SAF population. The Per Protocol population consisted of 31 subjects of the ITT population who completed the study. The study was terminated early because of efficacy risks and the PK parameters planned to be assessed in samples taken from the PK subset were not evaluated because no PK analysis was performed on the respective samples.

Screened population (and who signed the ICF): 169

Safety set (SAF) population: 142

Intent-to-treat set (ITT) population: 142

Per Protocol set (PP) population: 31

Reporting group values	Overall trial	Total	
Number of subjects	142	142	
Age categorical			
ITT/SAF group			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	104	104	
85 years and over	5	5	
Not collected - screenfailure	1	1	
Age continuous			
Units: years			
median	70.0		
full range (min-max)	45 to 89	-	
Gender categorical			
Units: Subjects			
Male	142	142	

End points

End points reporting groups

Reporting group title	Each enrolled subject received 10.8 mg Zoreline SC implant
Reporting group description:	
142 subjects started the treatment with Zoreline. The subjects had to come to the clinic center on Days 1, 2, 4, 8, 15, 29, 30, 36, 57, 84, and on Day 85 of Cycle 1 (=pre-dose on Day 1 of Cycle 2) and on Days 2, 4, 8, 15, 29, 36, 57, 84, and on Day 85 of Cycle 2 (which is the End of Treatment day). A total of 24 subjects were part of the pharmacokinetic (PK) substudy. This group had additional blood samples taken to assess the PK profile of the trial medication in addition to their blood collected for pharmacodynamic and safety assessments. Subjects in the PK substudy had seven additional visits on Days 22, 43, 45, 50, 64, 71 and 78 of Cycle 1. After all the PK substudy was not performed: the study was terminated early because of efficacy risks and the PK parameters were not evaluated because no PK analysis was performed on the respective samples. Each treatment cycle had a duration of 84 days. The total treatment duration of this trial was 168 days, two cycles.	

Primary: Pharmacodynamics

End point title	Pharmacodynamics ^[1]
End point description:	
Responder subjects are subjects for which a response was defined as the subject having serum testosterone levels ≤ 50 ng/dL on at least one of the sampling time points on consecutive days. This assessment was done on the Intention to Treat Population.	

The following values list the responder subjects of the ITT population N=142

End point type	Primary
End point timeframe:	
Cycle 1 Day 29 or 30; Cycle 1 Day 84 or Day 85; Cycle 2 Day 84 or 85	

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: Testosterone levels were planned to be determined for each subject from D1 of Cycle 1 to D85 of Cycle 2 (End of Treatment). Due to early termination of the trial, testosterone levels were evaluated for 42 subjects up to D85 of Cycle 1. The response rates are listed per time-point together with a 95% 2-sided CI (exact method).

End point values	Each enrolled subject received 10.8 mg Zoreline SC implant			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: responder subjects				
Cycle 1, Day 29/30	29			
cycle 1, Day 84/85	37			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics

End point title	Pharmacodynamics
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End point description:

Serum concentrations of testosterone.

Because of the early termination of the trial, no further planned efficacy, PK, and pharmacodynamic evaluations analysis were performed.

In the following section the median value for the change from baseline visit were added from the Intention to Treat population is listed.

With the between brackets the minimum and maximum value

Med (Min to Max)

End point type	Secondary
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End point timeframe:

Between D 1 and D 29 of Cycle 1, surge at re-injection and potential escape (surge) following the onset of suppression after the initial surge in Cycle 1 to Day 85 of Cycle 1 (pre-dose of Cycle 2) and after the surge at reinjection in Cycle 2 to Day (EoT)

End point values	Each enrolled subject received 10.8 mg Zoreline SC implant			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: ng/dL				
median (full range (min-max))				
Visit 3 - Cycle 1 Day 2	183.09 (67.820 to 572.41)			
Visit 4 - Cycle 1 Day 4	245.87 (-21.25 to 615.21)			
Visit 5 - Cycle 1 Day 8	22.820 (-278.2 to 329.42)			
Visit 6 - Cycle 1 Day 15	-294.2 (-664.4 to -112.9)			
Visit 8 - Cycle 1 Day 29	-340.2 (-920.8 to 71.090)			
Visit 9 - Cycle 1 Day 30	-360.7 (-915.2 to 103.03)			
Visit 10 - Cycle 1 Day 36	-374.2 (-946.0 to 36.790)			
Visit 14 - Cycle 1 Day 57	-389.5 (-958.3 to -143.5)			
Visit 18 - Cycle 1 Day 84	-389.4 (-958.2 to -67.40)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety
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End point description:

Clinical safety was addressed by recording AEs, physical examinations, weight, vital signs, electrocardiogram [ECG], laboratory assessments (hematology, biochemistry and urinalysis), ECOG, and concomitant medications/procedures.

The values listed below refer to the number of AEs.

End point type	Secondary
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End point timeframe:

From subject ICF signature until End of Treatment Visit.

End point values	Each enrolled subject received 10.8 mg Zoreline SC implant			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: Adverse Events	135			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Continuously from signing of ICF until the last trial related activity.

Please refer to the CSR for more details about type of AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Subjects affected by adverse events
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Reporting group description:

Overall, 169 subjects were screened and signed the ICF to participate in the trial (defined in this trial as the ENR population). Of these, 142 subjects were confirmed eligible on Cycle 1 Day 1, were enrolled in the trial and received at least one dose of trial medication (SAF population). The remainder of 27 subjects did not meet all eligibility criteria and were considered screen failures.

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Screened population (and who signed the ICF): 169

Safety set (SAF) population: 142

Intent-to-treat set (ITT) population: 142

Per Protocol set (PP) population: 31

Serious adverse events	Subjects affected by adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 142 (4.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Multiple injuries	Additional description: Polytrauma after car accident		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Transient Ischaemic Attack	Additional description: Transient ischemic accident		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Proctitis	Additional description: Acute paraproctitis		

subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion	Additional description: Prolaps L4/L5		
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal pain	Additional description: Pain lumbar spine		
alternative assessment type: Non-systematic			
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			
Urosepsis			
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: 5 %

Non-serious adverse events	Subjects affected by adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 142 (40.14%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	57 / 142 (40.14%)		
occurrences (all)	135		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2019	Protocol amendment V2.0, dated 06-Jun-2019: The main changes were: - The addition of exclusion criterion #10: Hypersensitivity to GnRH and its analogues, - The addition to the safety section 1.6, - The addition of explanation for study purpose in section 2.1 - The addition of explanation of expected adverse events in section 6.4.6

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.

Due to the early termination of the study only 31 patients could finish the study according to the protocol whereas the number of patients with intention to treat was 142.

Notes: