2 SYNOPSIS

TITLE OF TRIAL:

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.

PRINCIPAL INVESTIGATORS AND TRIAL CENTERS:

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PUBLICATION(S) BASED ON THE RESULTS OF THE TRIAL (REFERENCE):

- Not applicable.

TRIAL PERIOD:

First patient in:	14Jun2019
Last patient last visit:	06Apr2020

PHASE OF DEVELOPMENT: III

All objectives are per the clinical trial protocol version 2.0 dated 06Jun2019 (Appendix 16.1.1).

OBJECTIVES:

The primary objective was:

- To assess the ability of goserelin 10.8 mg (Zoreline) 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).

The secondary objectives were:

- To assess general safety and acceptability of the drug and syringe combination in line with standard of care.
- To characterize the goserelin plasma concentration profile (time to reach C_{max} [T_{max}], minimum plasma concentration [C_{min}], maximum plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC]) from Day 1 to Day 85 in each treatment cycle, i.e. during two consecutive treatment cycles in which Day 85 represents the end of treatment of each cycle. The area under the curve was planned to be extrapolated to infinity ($AUC0_{-\infty}$) and terminal (apparent elimination) half-life ($t_{½}$) was planned to be determined.
- To characterize the testosterone serum concentration profile (C_{max}, AUC) including initial surge between Day 1 and Day 29 of Cycle 1, time to achieve castration level, acute on chronic phenomenon, surge at re-injection and potential escape (surge) following the onset of suppression after the initial surge.

The exploratory objectives were:

- To evaluate luteinizing hormone (LH) and follicle-stimulating hormone (FSH) serum concentration from Day 1 of Cycle 1 to Day 85 of Cycle 2 (End of Treatment).
- To evaluate Prostate-Specific Antigen (PSA) serum concentration at Day 1, 29 and 85 of Cycle 1 and Day 85 of Cycle 2 (End of Treatment).
- To assess the ability of Zoreline 10.8 mg subcutaneous implant to induce testosterone serum suppression below ≤20 ng/dL.
- To assess the performance of a novel syringe used to inject Zoreline 10.8 mg implant.

TRIAL DESIGN:

This was a Phase III open-label, multi-center trial to assess the pharmacodynamics, pharmacokinetics and safety of 10.8 mg goserelin (Zoreline) subcutaneous (SC) implant in male subjects with prostate cancer.

Overall, 17 trial sites in multiple countries in Europe were considered for conducting the

trial, with 14 sites ultimately recruiting the trial subjects. In total, 169 subjects were screened and signed the informed consent form (ICF) for participation in this trial, with 142 subjects meeting all eligibility criteria (enrolled population) and starting 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.

Each enrolled subject received the 10.8 mg goserelin (Zoreline) SC implant.

Each treatment cycle had a duration of 84 days. The total treatment of this trial had a duration of 168 days, two cycles. On Day 1 of Cycles 1 and 2 (Day 85 of Cycle 1 is Day 1 of Cycle 2), subjects received an SC implant of 10.8 mg goserelin (Zoreline). An End of Treatment Visit (Day 85 of Cycle 2, Day 168) was performed 84 days after the last dose (±2 days).

The end of trial was defined as the last subject last visit (LSLV). For the purposes of data summarization, data analyses were performed after the last subject completed the End of Treatment Visit.

NUMBER OF SUBJECTS (ANALYZED):

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

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.

All eligibility criteria are per the clinical trial protocol version 2.0 dated 06Jun2019 (Appendix 16.1.1).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Inclusion criteria:

To be eligible to participate in this trial, subjects had to be males ≥ 18 years, with total testosterone levels > 250 ng/dL, a prostate serum albumin (PSA) level of ≥ 4 ng/dL (excluding subjects with previous prostatectomy and/or prostate radiotherapy, for which all PSA levels were allowed), with a life expectancy >1 year, an Eastern Cooperative Oncology Group (ECOG) score ≤2 and with histologically confirmed prostate adenocarcinoma and indicated for androgen deprivation therapy (ADT). This included but was not limited to subjects suffering from localized intermediate-risk or high-risk prostate cancer (having a clinical state of T2b and ≥T2) and subjects with locally advanced prostate cancer (having

T3-4 as clinical state [Mottet, 2018; NICE Guideline, 2014]). Previous prostatectomy and/or prostate radiotherapy was allowed.

Exclusion criteria:
Candidates were excluded from trial entry they had hormonal treatment for prostate cancer (surgical castration or other hormonal manipulation, including gonadotrophin-releasing hormone [GnRH] receptor agonists, GnRH receptor antagonists, anti-androgens, estrogens, 5 alpha reductase inhibitors) within 6 months prior to the screening visit (with a maximum of 2 previous treatment cycles allowed in case of GnRH analog treatment), were scheduled for prostatectomy, chemotherapy or prostate radiotherapy during the trial period, had alanine aminotransferase (AL) or aspartate transaminase (AST) ≥ 2x upper limit of normal (ULN), had an estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 at screening visit, had an unstable medical condition or chronic disease, had a history of severe uncontrolled asthma, anaphylactic reactions, severe urticaria and/or angioedema, and (history of) hypersensitivity to GnRH and its analogoues, or had received an investigational drug within the last 28 days before Visit 2 (Cycle 1 Day 1).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Subjects eligible for the trial received the 10.8 mg goserelin (Zoreline); the 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). No dosage adjustment was performed for subjects with renal or hepatic impairment, or in the elderly.

All sites received 10.8 mg goserelin (Zoreline) from the same investigational medicinal product (IMP) batch (batch/lot number 18EAD004-01).

REFERENCE THERAPY PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

None applicable.

TRIAL DURATION:

A screening period occurring from Day -7 to Day -1 before the first trial medication administration (i.e., on Day 1 of Cycle 1) was planned. The subjects had to come to the clinical center on Days 1, 2, 4, 8, 15, 29, 30, 36, 57, 84, 85 of Cycle 1, pre-dose on Day 1 of Cycle 2, and on Days 2, 4, 8, 15, 29, 36, 57, 84, 85 of Cycle 2 (End of Treatment). The duration of treatment was 168 days.

STATISTICAL METHODS:

Typical responder rates (subjects achieving serum testosterone levels below the castration level; ≤ 50 ng/dL) after goserelin subcutaneous implants range between 96 and 100%. Assuming a true response rate of 98% on Cycle 1 Day 29, of 97% on Cycle 1 Day 85 and of 99% on Cycle 2 Day 85, a sample size of 120 evaluable subjects would have provided 80%

power to demonstrate that the response rate is higher than 90% at each time point with a two-sided significance level of α=0.05.
Overall, 169 subjects were screened and signed the ICF to participate in the trial; 142 subjects were treated with goserelin; this led to a screening failure of 16%. Any drop-out subjects were not replaced.

PK substudy:
The sample size for the analysis of goserelin and testosterone pharmacokinetics, as secondary objective, was established at 24 subjects. This sample size was not statistically based.

Primary objective:
The primary objective was addressed using the ITT population. The responder rate proportion of subjects achieving serum testosterone levels below the castration level (≤ 50 ng/dL) had to be independently estimated at Day 29 of Cycle 1, at Day 85 of Cycle 1 and at Day 85 of Cycle 2 together with a 95% 2-sided confidence interval (CI) (exact method). A sensitivity analysis was planned to be performed on the PP population.

Secondary objectives and exploratory objectives:
The secondary and exploratory objectives had to be addressed using the ITT and PP populations. Safety evaluation was assessed using the SAF. The statistical evaluation was descriptive using standard statistical tools, including (geometric) mean, standard deviation (SD), median, maximum, minimum, range, coefficient of variation (CV%). The statistical tools used were appropriate to the statistical distribution of the secondary variables.

The Statistical Analysis Plan (SAP, V1.0 dated 29Jan2021; Appendix 16.1.2) describes specific statistical analysis details.

TRIAL SUBJECTS:
Informed consent was obtained from 169 screened subjects between 12Jun2019 and 12Dec2019, before the Independent Data Review Committee (IDMC) provided the recommendation to stop the trial, which was implemented by the sponsor (. Due to early termination of the trial, not all the data collected during the trial had been fully (100%) monitored and reviewed according to the standard operating procedures (SOPs) of the clinical research organization (CRO) performing the trial (see SAP V1.0 dated 29Jan2021 [Appendix 16.1.2] for a detailed explanation on data monitoring and review, as well as the information regarding the data that was monitored and reviewed).

The SAF population consisted of 142 subjects (enrolled subjects) who received at least one dose of trial medication (the number of subjects who received both planned doses of trial medication was 77). The ITT population consisted of 142 subjects who received trial medication and had at least one post-baseline assessment of any type. The PP population consisted of the 31 subjects of the ITT population who completed the treatment period and excluded subjects with major protocol deviations (Subjects 08-005, 14-001 and 20-023).

Overall, three major protocol deviatios were recorded, two at screening and one during trial treatment. At screening, two subjects had protocol deviations regarding eligibility criteria

(Subject 08-005 did not meet inclusion criterion 5 and Subject 14-001 met exclusion criterion 4), but were still included in the ENR and SAF populations. During treatment, one subject (Subject 20-023), who was included in all trial populations, had missed assessments/visits due to personal reasons. No protocol deviations were recorded due to coronavirus disease 2019 (COVID-19).

EFFICACY, PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

The ability of 10.8 mg goserelin (Zoreline) subcutaneous implant to induce testosterone serum suppression (≤50 ng/dL) in male subjects with prostate cancer was analyzed at Day 29 and Day 30 (Day 29/30) and at Day 84 and Day 86 (Day 84/86) of Cycle 1 in the ITT population. The first analysis occurred after 40 subjects completed Day 85 of Cycle 1 (as pre-defined in Appendix 16.1.7), to enable the IDMC to provide a recommendation regarding trial continuation. The number of non-responders (defined as having a serum testosterone concentration >50 ng/dL) recorded in the ITT population at Cycle 1 Day 29/30 was 13 subjects. Per the specifications stated in the clinical trial protocol (Appendix 16.1.1) to stop the trial as soon as at least eight non-responders were observed at any specific timepoint in the ITT population, and following the recommenations of the IDMC after reviewing the Day 29/30 and Day 84/85 data from the first 40 subjects, the trial was terminated (Appendix 16.1.7). No other secondary and exploratory endpoints were assessed, except for testosterone serum concentrations at Day 29/30 and Day 84/86 of Cycle 1, occurrence of adverse events (AEs) and performance of a novel syringe used to inject the implant.

SAFETY RESULTS:

Overall, 135 AEs were reported in 57 subjects of 142 total subjects of the SAF population (40.1%), of which all but one AE (134 AEs in 56 subjects of the SAF population [39.4%]) were considered treatment emergent adverse events (TEAEs). A total of seven Grade 3 TEAEs were encountered in six subjects of the SAF population (4.2%): two TEAEs of hypertension in Subjects 04-002 and 20-032, one TEAE of urosepsis and one of hydronephrosis in Subject 08-006, one TEAE of pelvic pain in Subject 30-012, one TEAE of angina pectoris in Subject 40-001 and one TEAE consisting of multiple injuries in Subject 20-004. No Grade 4 or Grade 5 TEAEs were recorded during the trial. Except for Grade 3 hypertension in Subject 04-002, concomitant or additional treatment was given in the case of all other Grade 3 TEAEs; at the end of the trial, the outcome for these TEAEs was considered as recovered for all except pelvic pain.

In total, six serious TEAEs were recorded in five subjects of the SAF (2.5%); four serious TEAEs in three subjects (2.1%) were of Grade 2 (proctitis in Subject 40-022, intervertebral disc protrusion and spinal pain in Subject 07-001, transient ischemic attack in Subject 20-029) and two serious TEAEs in two subjects (1.4%) were of Grade 3 (urosepsis in Subject 08-006 and multiple injuries in Subject 20-004). For all of these serious TEAEs, concomitant or additional treatment was given; the outcome was recorded as recovered, except for spinal pain, where the outcome was recorded as recovered with sequelae. None of the serious TEAEs recorded during the trial was related to the trial medication.

In total, 68 TEAEs defined as related to the trial medication were recorded in 38 subjects of the SAF population (26.8%), including hot flushes (18 TEAEs in 16 subjects, 11.3%),

injection site discomfort (one TEAE in one subject, 0.7%), paresthesia (three TEAEs in two subjects, 1.4%), and hyperhidrosis (five TEAEs in five subjects, 3.5%). Of the related TEAEs, only one Grade 3 TEAE (angina pectoris recorded in Subject 40-001) was recorded. No action was taken towards the trial medication, the subject received concomitant or additional treatment, and the outcome was recorded as recovered.

The only common TEAEs (>5%; defined in this trial differently than the defintion used in the SmPC of the original goserelin product Zoladex®; SmPC Zoladex, 2019) encountered during the trial in the SAF population were of hot flushes (18 trial drug-related Grade 1 TEAEs in 16 subjects [11.3%]). No drug discontinuations were recorded due to TEAEs. No deaths occurred during the trial.

Physical examination, electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG) performance status evaluations were performed only at screening. No clinically significant abnormalities were recorded in any of the subjects from the SAF population for any of the physical examination parameters analyzed. In terms of ECG, 85 subjects of the SAF population (59.9%) had normal ECG values and the remaining 57 subjects (40.1%) had abnormal not clinically significant ECG values at screening (still eligible). In terms of ECOG performance status, 88 subjects of the SAF population (62.0%) had an ECOG performance stats of 0, 43 subjects (30.3%) had an ECOG performance status of 1, and 11 subjects (7.7%) had an ECOG performance status of 2 at screening.

Clinical laboratory evaluations and vital signs' assessments were also performed. Overall, 33 clinically significant laboratory abnormalities were encountered in seven subjects of the SAF (5.0%). No clinically significant changes in vital signs were recorded during the trial.

Lastly, syringe performance, including the use of a local anesthetic prior to the use of the syringe for implant administration, was evaluated in a questionnaire to the investigators. A local anesthetic was used for two subjects (1.4%) of the SAF population during Visit 2 (Day 1 of Cycle 1) and for none of the 77 subjects during Visit 19 (Day 1 of Cycle 2) (54.2% of the total SAF). The injection (for SC placement) was successful for all subjects during Day 1 of Cycle 1 and for all 77 subjects receiving the trial drug during Day 1 of Cycle 2 (54.2% of the total SAF population). The injection was "difficult" for five subjects of the SAF (3.5%) during Day 1 of Cycle 1 and for two of the 77 treated subjects (1.4% of the SAF) during Day 1 of Cycle 2. The syringe needle security activation was complete and the injection was performed according to instructions for all subjects of the SAF during Day 1 of Cycle 1 and for all 77 subjects treated during Day 1 of Cycle 2 (54.2% of the SAF), therefore no injection-related AEs were recorded at these two timepoints. "Disagree" was recorded in terms of satisfaction with syringe use for two subjects (1.4%) during Day 1 of Cycle 1 and for one of the 77 subjects treated during Day 1 of Cycle 2 (0.7% of the SAF). Based on the data described above, the syringe performance was similar at Visit 19 as compared to Visit 2.

OVERALL CONCLUSIONS:

This clinical trial was terminated based on the specifications put forward in the clinical trial protocol regarding the primary objective, and in line with the corresponding statistical analysis performed.

Zoreline (10.8 mg goserelin) subcutaneous treatment of subjects with prostate cancer enrolled in this trial was safe. During treatment with Zoreline in this trial, hot flushes, injection site discomfort, paresthesia, and hyperhidrosis were encountered. These AEs were previously reported for Zoladex® as well (SmPC Zoladex, 2019). The only common (>5%)

trial-drug related TEAEs encountered with Zoreline in this trial were hot flushes (18 Grade 1 TEAEs in 16 subjects) at an incidence of 11.3%, lower than that encountered with the same compound in previous clinical trials (27.6% in the No0002-C201 trial, which evaluated one cycle of 10.8 mg Zoreline implant, and 28.9% in the 0080CA002 trial, which evaluated two cycles of 10.8 mg Zoreline implant; see Appendix 16.1.4).

While several types of AEs were encountered with both Zoreline and Zoladex® treatment (see SmPC Zoladex, 2019), the frequencies of the AEs encountered with Zoreline were substantially lower than those previously reported for Zoladex®, with the observation that a lower number of subjects were exposed to Zoreline in this trial (see Section 12.3). The only Zoreline-related Grade 3 TEAE (angina pectoris) that occurred in this trial had the outcome recorded as recovered after concomitant/additional treatment was given.

Taken together, the results obtained with the Zoreline depot used in this trial indicate that safety was ensured for all subjects. The low frequencies of AEs encountered with Zoreline in this trial might indicate apromising safety profile, with the specification that the number of subjects exposed to Zoreline in this trial represents a limitation to these conclusions.

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