SYNOPSIS

NAME OF SPONSOR/COMPANY

FERRING Pharmaceuticals A/S, Denmark (Cohort I)
FERRING Arzneimittel GmbH, Germany (Cohort II)

TITLE OF TRIAL

An Open-Label, Multi-Centre, Uncontrolled, Exploratory Trial Investigating Degarelix One-Month Dosing Regimen as Second-Line Hormonal Treatment after PSA-Failure in GnRH Agonist Treated Patients with Prostate Cancer

SIGNATORY INVESTIGATOR

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TRIAL SITE(S)

- Urologische Praxis, Bautzen, Germany (Cohort I)
- Urologische Praxis, Berlin, Germany (Cohort I)
- Urologische Klinik, Berlin, Germany (Cohort I & Cohort II)
- Urologische Praxis, Borken, Germany (Cohort I & Cohort II)
- Urologische Praxis, Erkrath - Hochdal, Germany (Cohort II)
- Urologische Praxis, Hagenow, Germany (Cohort I & Cohort II)
- Martini Klinik, Hamburg, Germany (Cohort I & Cohort II)
- Urologische Praxis, Husum, Germany (Cohort I)
- Urologische Praxis, Kirchheim, Germany (Cohort II)
- Urologische Praxis, Köln, Germany (Cohort II)
- Urologische Praxis, Lauenburg/Elbe, Germany (Cohort I & Cohort II)
- Urologische Praxis, Leipzig, Germany (Cohort II)
- Urologische Praxis, Markkleeberg, Germany (Cohort I & Cohort II)
- Urologische Klinik, Planegg, Germany (Cohort I)
- Wissenschaftskontor Nord, Rostock, Germany (Cohort I & Cohort II)

PUBLICATION (REFERENCE)

N/A

TRIAL PERIOD	**CLINICAL PHASE**
Cohort I: First patient first visit: 24-Jul-2008 Last patient last visit: 22-Sep-2009 **Cohort II:** First patient first visit: 03-May-2010 Last patient last visit: 29-December 2011	II

OBJECTIVES

Primary Objective

- To study whether treatment with degarelix may stabilise or reverse PSA progression in patients with prostate cancer (PCa) after failure of GnRH agonist treatment

Secondary Objectives

- To investigate testosterone control
- To investigate LH/FSH control
- To investigate PSA progression
- To investigate overall survival
- To investigate drug safety of degarelix

ENDPOINTS

Primary Endpoint(s)

Proportion of patients showing decreasing or stable PSA, defined as a relative change from baseline ≤ +10% of baseline PSA level, after three months of treatment

Secondary Endpoint(s) Cohort I

- Proportion of patients at testosterone castrate level defined as ≤0.5 ng/mL
- Serum levels of testosterone, PSA, LH, and FSH over time
- PSA progression free survival
- Overall survival time

Secondary Endpoint(s) Cohort II

- **Proportion of patients showing decreasing or stable PSA, defined as a relative change from baseline ≤ +10% of baseline PSA level, after one and/or two months of treatment**
- Proportion of patients at testosterone castrate level defined as ≤0.5 ng/mL
- **Proportion of patients at testosterone levels ≤0.2 ng/mL and ≤0.32 ng/mL**
- Serum levels of testosterone, PSA, LH, and FSH over time
- PSA progression free survival
- Overall survival time

METHODOLOGY

The trial was designed as an uncontrolled exploratory, multi-centre, open-label trial to evaluate efficacy of degarelix as a second line hormonal treatment.

In total, up to 14 visits, including the screening visit, were scheduled for each patient. A visit was scheduled on a monthly basis.

A starting dose of 240 mg of degarelix at a concentration of 40 mg/mL was given on Day 0 as two 120 mg s.c. injections. Thereafter, a maximum of 11 doses of 80 mg degarelix at a concentration of 20 mg/mL were given 28 days apart via single s.c. injections.

Dosing Frequency	Degarelix Dose (concentration)	Injection Volume	Administration
Starting Dose Day 0	240 mg(40 mg/mL)	2 x 3.0 mL	s.c.
Maintenance Therapy up to 12 months	80 mg (20 mg/mL)	1 x 4.0 mL	s.c.

The trial was planned to be conducted in two phases with two separate cohorts each. If at least 20% of the patients in the first cohort had reached the primary endpoint after three months (defined as a stable and decreasing PSA ≤+10% from Baseline), a second cohort was to be included.

The decision to continue with the second cohort was to be taken at an interim analysis meeting with at least the Coordinating Investigator, Trial Statistician, and Medical Adviser being present.

Analysis of the results of the first cohort showed that four out of 24 patients (i.e. 16.7%) in the intention-to-treat (ITT) population had a stabilised or reversed PSA progression according to the pre-set criterion. During an interim analysis meeting it was therefore decided not to include a second cohort of patients in this trial.

However, during post-meeting discussions it was later decided to continue with a second cohort even though the pre-set criteria were not fulfilled. The design of cohort II was adjusted in Amendment 02.

Substantial Amendments

No.1 (11. November 2008)

- Additional Withdrawal Criterion: The patient shows no response to treatment (change in PSA level > + 10% of baseline PSA level)
- Removal of section within 8.1.2 Collection and Recording of Adverse Events

No. 2 (05. October 2009)

- Inclusion criterion No. 4 clarified
- Inclusion criterion No. 6 changed: Testosterone **≥0.32 ng/mL** at inclusion
- Inclusion criterion No. 9 deleted
- Two additional secondary endpoints:
  - Proportion of patients showing PSA values of ≤ +10% vs. baseline after 1 and/or 2 months.
  - **Proportion of patients at testosterone levels ≤0.2 ng/mL and ≤0.32 ng/mL**
- Transfer of Sponsorship from FERRING Pharmaceuticals to FERRING Arzneimittel, Germany

No. 3 (18. November 2010)

- Inclusion criterion No. 6 changed: Testosterone **≥0.2 ng/mL** at inclusion.

NUMBER OF SUBJECTS

Cohort I
Twenty five (25) patients were allocated a Patient number and all of them actually received trial medication. One patient did not have any efficacy assessment after dosing.

Cohort II
Twelve (12) patients were allocated a Patient number and all of them actually received trial medication.

MAIN CRITERIA FOR INCLUSION / EXCLUSION

Patients with histologically confirmed PCa who was hormone refractory after primary hormonal treatment could be investigated in this trial if the eligibility criteria were fulfilled.

Inclusion Criteria Cohort I

1. Patient had given written informed consent before any trial-related activity was performed.
2. Patient was 18 years or older.
3. Histologically confirmed PCa.
4. Patient had received GnRH receptor agonist therapy for a duration of at least 12 months (the last dose of GnRH agonist must had been received before Visit 1).
5. Patient had experienced rising PSA levels although receiving GnRH receptor agonist therapy, defined as two consecutive rises of PSA at least two weeks apart in two 50% increases over the nadir, and at least one PSA value of >2.5 ng/mL within the last six months.
6. Testosterone on castrate level (defined as ≤0.5 ng/mL).
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
8. Estimated life expectancy at least 12 months.
9. For the second cohort: patients must have had undergone radical prostatectomy (not applicable)

Inclusion Criteria Cohort II

1. Patient has given written informed consent before any trial-related activity is performed.
2. Patient is 18 years or older.
3. Histologically confirmed prostate cancer.
4. Patient has received GnRH receptor agonist therapy for a duration of at least 12 months **(the first dose of GnRH-antagonist is to be administered when the next dose of the GnRH-agonist would have been due).**
5. Patient has experienced rising PSA levels although receiving GnRH receptor agonist therapy, defined as two consecutive rises of PSA at least two weeks apart in two 50% increases over the nadir, and at least one PSA value of >2.5 ng/mL within the last six months.
6. Testosterone **≥0.32 ng/mL** at inclusion
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
8. Estimated life expectancy at least 12 months as judged by the investigator.
9. **./.**

Exclusion Criteria

1. Previous history or presence of another malignancy, other than PCa or treated squamous / basal cell carcinoma of the skin, within the last five years.
2. Ongoing GnRH agonist therapy (last dose of previous GnRH receptor agonist must had to be before Visit 1).
3. Any pre-trial secondary hormonal manipulation (including antiandrogens) after PSA increase as described as above and before trial entry. Antiandrogens as part of complete androgen blockade had to be discontinued at least three months before first dose of trial medication.
4. Previous or current treatment with chemotherapy (e.g. estramustin) for PCa.
5. Known hypersensitivity towards any component of the investigational medical product.
6. History of severe uncontrolled asthma, anaphylactic reactions, or severe urticaria and/or angioedema.
7. Known or suspected clinically significant liver and/or biliary disease.
8. Any clinically significant laboratory abnormalities, disorders, or other condition including alcohol or drug abuse, which may have affected the patient's health or the outcome of the trial as judged by the Investigator.
9. Patient had a clinically significant disorder (other than PCa) including but not limited to renal, haematological, gastrointestinal, endocrine, cardiac, neurological, or psychiatric disease, and alcohol or drug abuse or any other condition, which may have affected the patient's health or the outcome of the trial as judged by the Investigator.
10. Patient had a mental incapacity or language barriers precluding adequate understanding or cooperation.
11. Patient had received an investigational drug within the last 28 days preceding screening visit. Or longer if considered to possibly influence the outcome of the current trial.
12. Previous participation in any degarelix trial.

Discontinuation Criteria

The patient had to be discontinued from the trial if:

- The Investigator judged it necessary due to medical reasons
- The patient received prohibited therapy or procedures
- The patient wished to discontinue for any reason

In addition, the patient had to be discontinued from the trial during Month 3 - 12 if:

- The patient showed no response to treatment (change in PSA level > +10% of Baseline PSA level)

MEDICINAL PRODUCTS

Degarelix was given as s.c. injections. Degarelix was supplied as a freeze-dried powder for suspension for injection, in vials of 80 mg and 120 mg. Degarelix was reconstituted with Water for Injection to a concentration of 20 or 40 mg/mL.

Batch Numbers

Vials	Batch Numbers Cohort I	Batch Numbers Cohort II
Degarelix – 80 mg (20 mg/mL)	07I19-01	08E19-01, CE0349,
Degarelix – 120 mg (40 mg/mL)	07I11-01	07I11-01, 08C10-01, CE0351
Water for Injection	7370040	5019, 36057, 737004

DURATION OF TREATMENT

The duration of treatment was maximum one year.

TRIAL PROCEDURES / ASSESMENTS

Blood samples for analyses of PSA were collected at each visit. Samples for analysis of testosterone, LH, and FSH were taken at Visit 1-5, 8, and End of Trial Visit. At dosing visits, the blood sampling were taken pre-dose. Analysis was performed by a central laboratory.
PSA and Testosterone values used for confirmation of inclusion criteria 5 and 6 were based on local laboratory results and were available for source data verification.

STATISTICAL METHODS

All analyses were performed and summary statistics calculated using SAS version 9 or higher. The populations for analysis were:

- The ITT analysis set comprised of data of all patients who received at least one dose of degarelix and had at least one efficacy assessment after dosing.
- The per protocol (PP) analysis set comprised patients included in the ITT analysis set without any major protocol deviations
- The safety analysis set comprised of all patients who received at least one dose of degarelix.

The primary efficacy endpoint was analysed for both the ITT and PP analysis sets, with the ITT analysis set considered primary. For the primary endpoint the percent change in the PSA level from Baseline to 3 months of treatment (Visit 5) or the last available visit (i.e. Last Observation Carried Forward [LOCF]) within the first three months was used to assess if a treatment response was present. Due to the extreme between-patient variability of PSA levels all values are expressed in % change from Baseline. The individual changes were determined, summarised with descriptive statistics and classified as to whether a treatment response was present or not, response being defined as

Response (stabilisation or decrease):	Difference ≤ +10% of Baseline level
No response (increase):	Difference > +10% of Baseline level

All secondary efficacy endpoints were analysed for both the ITT and PP analysis sets, unless otherwise stated. The change and percent change from Baseline to each visit for serum levels of testosterone, PSA, LH, and FSH and the proportion of patients at castrate level was summarised with descriptive statistics. The Baseline was defined as the last value obtained at the last assessment prior to the first dose of degarelix.
The time to the first occurrence of PSA progression, defined as PSA > +10% from Baseline, was defined as the number of days from the first dose of trial drug to the first event of PSA progression. Baseline value was defined as the value before and closest to first day of degarelix. If a patient had not experienced PSA progression at the End of the Trial or before otherwise discontinuing the trial, then that patient's data were censored at the date of last visit. PSA progression free survival was estimated using Kaplan-Meier methodology. The number of patients who experience PSA progression and number of patients that complete the trial without experiencing PSA progression was summarised. The median of the event free time and its 95% confidence interval is provided.
There were no deaths observed during the trial and therefore the proposed secondary endpoints of overall survival time was not calculated.
For the safety endpoints, standard summary tables were prepared and if appropriate were also presented graphically.

Cohort I

- Twenty five (25) patients were allocated a Patient number and all of them actually received trial medication. One patient did not have any efficacy assessment after dosing. The ITT analysis set therefore comprised 24 patients.
- Four patients in the ITT analysis set had at least one major protocol deviation and were excluded from the PP analysis. Thus, 20 patients were included in the full PP analysis set. In addition, one patient had a major protocol violation which occurred at Visit 7. Therefore, for this patient only the data up to and including Visit 6 were used in the PP analysis. Thus, he was included in the primary analysis after 3 months.
- The safety analysis set comprised 25 patients.

Cohort II

- Twelve (12) patients were allocated a Patient number and all of them actually received trial medication. The ITT analysis set comprised 12 patients.
- 10 patients were included in the PP analysis set due to major protocol violations.
- The safety analysis set comprised 12 patients.

EFFICACY RESULTS

Cohort I:

The proportion of patients who had a decreasing or stable PSA (i.e. a relative change from Baseline ≤+10%), after three months of treatment was four out of 24 patients (i.e. 16.7%). However, one of these patients discontinued from the trial already before the three-month Visit. He was therefore not included in the OC analysis and, hence, the proportion was 15% (three patients out of 20). In the PP analysis set, two out of 20 patients (10.0%) in the LOCF and two out of 18 (11.1%) in the OC analysis fulfilled the criterion for treatment response.

Hence, depending on which data set that was investigated, the percentage of responders varied between 10.0 and 16.7%. This apparently wide range is not unexpected given the low number of patients and, nevertheless, all responders rates were below the pre-set criterion for success (i.e. <20%).

The serum levels of testosterone were in all 24 patients at castrate levels (≤0.5 ng/mL) throughout the trial and only small changes in the median serum levels of testosterone as compared to the Baseline values were noted.

The median serum levels of PSA increased during the first three months of treatment as compared to the Baseline value. After the three-month visit, however, when a majority of the patients had discontinued treatment, the median serum levels of PSA decreased with about 75% as compared to the Baseline values. The PSA levels were sustained at this low level until the EoT visit.

The median serum levels of LH were below the limit of detection in the majority of cases. The median serum levels of FSH decreased with about 40% as compared to the Baseline values at the 1-month visit and were kept at this low level for the rest of the trial (i.e. from the 1-month visit to the EoT visit).

In the ITT analysis set, there were 21 patients with PSA progression (defined as PSA >+10% from Baseline). Most of the PSA progressions occurred around Day 28 (i.e. at Visit 3). The probability of completing the trial without experiencing PSA progression was 8.77% (95% CI: 1.51; 24.3%). Similar results were observed for the PP analysis set.

Cohort II:

Four patients (33.33% [95% CI: 9.92–65.11%]) responded to treatment with degarelix as they showed decreasing or stable PSA, defined as a relative change from baseline ≤+10% of baseline PSA level, after 3 months of treatment using LOCF (ITT). The proportion of patients with response was 44,44% [95% CI: 13.70–78.80%] at Month 3 when using observed case results in the ITT. In the PP analysis set, 4 out of 10 patients (40.00%) in the LOCF and 4 out of 9 (44,44%) in the OC analysis fulfilled the criterion for treatment response.

Hence, depending on which data set that was investigated, the percentage of responders varied between 33.3 and 44.4%. The responder rates for the small sub-population of patients investigated in cohort 2 were above the pre-set criterion for success (i.e. <20%). The proportion of patients showing response was 67% after one month and 40% after 2 months of treatment with degarelix when using observed case results in the ITT.

The number of patients at testosterone castrate levels defined as ≤ 0.5 ng/mL, ≤ 0.32 ng/mL or ≤ 0.2 ng/mL was 11, 9 and 8, respectively. There were only minor median changes from baseline in the testosterone levels of patients who remained in the study.

There were only minor median changes from baseline in the PSA levels of patients who remained in the study.

No median change from baseline was observed in LH levels of patients who remained in the study until Day 112 and a slight increase on Days 168 and 336. The FSH levels of patients who remained in the study tended to decrease over time until Day 112 and returned to near baseline level until Day 336.

In the ITT analysis set, there were 11 patients with PSA progression (defined as PSA >+10% from Baseline). The estimated probability of no PSA failure was 75% (95% CI: 40.8–91.2%) after 1 month and 42% (95% CI: 15.2–66.5%) after 2 months of treatment with degarelix. The probability of completing the trial without experiencing PSA progression was 8.3% (95% CI: 0.5; 31.1%).

SAFETY RESULTS

The overall safety profile of the degarelix treatment regimens was considered good and in line with previous degarelix studies.

Cohort I:
Overall, 18 patients reported treatment-emergent AEs. The most frequently reported treatment-emergent AEs were injection site reactions such as injection site erythema and injection site swelling. 14 patients reported ADRs; the most common ADRs were injection site erythema, injection site swelling, injection site pain, injection site induration, and hot flush. Most AEs were mild (in 14 patients) or moderate (8 patients) in intensity. The severe AEs included hypokalaemia, colon cancer, carotid artery stenosis, bladder tamponade, and pleural effusion (each event reported once). No deaths occurred during this trial.

Three patients reported treatment-emergent SAEs during the trial. All SAEs were assessed by the Investigator as unrelated or unlikely to be related to degarelix.

One patient discontinued due to an AE (carotid artery stenosis), this AE was reported as an SAE.

The mean changes in clinical chemistry and haematology parameters from Baseline to EoT were overall small. The largest mean changes were noted for serum ALT (9.15% decrease) and serum alkaline phosphatase (12.0% increase).

For the liver function laboratory parameters, the percentage of patients with shifts from normal/low at Baseline to high at any time-point was 9% for alkaline phosphatase, 5% for AST, and 0% for ALT and GGT. Only one of the patients had an elevation in serum bilirubin at any time-point (at Visit 2, i.e. before dosing of degarelix) and no patients had serum bilirubin levels >1.5 x ULN.

A high reported incidence of pre-specified markedly abnormal decrease in haematocrit (38%) was an expected haematological change for drugs that reduce testosterone levels.

The incidence of markedly abnormal changes in renal function parameters was low in this trial. There was no evidence that exposure to degarelix was associated with drug-induced renal injury. There was only one patient with markedly abnormal increases in urea nitrogen (>10.7 mmol/L) and there was no evidence that exposure to degarelix was associated with drug-induced renal injury.

One patient had an increase in body weight of ≥7% from Baseline. Over the course of the trial the mean increase in body weight was 0.27 kg.

There were small mean changes in the systolic (-4.10 mmHg), diastolic (-1.38 mmHg) blood pressures and in heart rate (mean change 1.67 bpm) from Baseline to the EoT. No patients had any markedly abnormal changes in vital signs at any time-point.

No patients had any abnormal, clinically significant ECG alterations at either Screening or at the EoT Visit.

One patient had an abnormal, clinically significant physical examination finding (suspected bone metastases) at the EoT Visit and four patients had abnormal, not-clinically significant physical examination finding. All of these findings were present at Screening.

Cohort II:
Administration of degarelix over 12 months was generally well tolerated with a total of 34 mostly mild or moderate TEAEs in 10 (83%) patients. A total of 7 patients (58%) reported 15 ADR, which all consisted of injection site erythema and injection site swelling.

There were 2 treatment-emergent SAEs in one patient (anaemia and anaemia of malignant disease), which were both classified as being severe and not related to IMP.

No patient died or discontinued due to an adverse event.

None of the few markedly abnormal changes in laboratory parameters was considered to be clinically significant or an AE.

A weight gain in one patient was considered to be a mild AE that was not related to IMP.

There was no clinically significant abnormal ECG at End of Trial and no ECG worsened from screening.

CONCLUSIONS

From the present open-label, multi-centre, uncontrolled, exploratory trial in PCa patients investigating degarelix one-month dosing regimen as second-line hormonal treatment after PSA-failure following GnRH agonist treatment the following conclusions can be drawn:

Cohort I:

- The response rate was below the pre-set criterion for success (defined as at least 20% of patients showing decreasing or stable PSA after three months of treatment); the proportion of patients in the ITT analysis set who had a decreasing or stable PSA after three months of treatment using the LOCF methodology was four out of 24 patients (i.e. 16.7%).
- The overall safety profile of the degarelix treatment regimens was considered good and in line with previous degarelix studies.

Cohort II:

- All safety findings were in line with previous degarelix trials and expected for this group of elderly PCa patients with a high frequency of medical history of cardiac disease or hypertension being treated with androgen deprivation therapy. It can therefore be concluded that the overall safety profile of the degarelix treatment was good and in line with previous degarelix studies.

FE 200486 CS27 has to be considered as an exploratory, hypothesis-generating trial for further controlled studies in this patient population.

However, within the patient collective under investigation in cohort 2 a relatively high number of patients reached the primary endpoint. About one third of the patients seemed to benefit from the treatment with Degarelix.