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Prostate Cancer

Degarelix: A Novel Gonadotropin-Releasing Hormone (GnRH) Receptor Blocker—Results from a 1-yr, Multicentre, Randomised, Phase 2 Dosage-Finding Study in the Treatment of Prostate Cancer

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Abstract

Background: Degarelix is a gonadotropin-releasing hormone antagonist (GnRH receptor blocker) with immediate onset of action, suppressing gonadotropins, testosterone, and prostate-specific antigen (PSA) in prostate cancer.
Objective: To determine the efficacy and safety of initial doses of 200 mg or 240 mg of degarelix and thereafter monthly subcutaneous maintenance doses of 80 mg, 120 mg, or 160 mg of degarelix for the treatment of prostate cancer.
Design, setting, and participants: The 1-yr study was of open-label, randomised design and involved 187 patients (range: 52–93 yr, median: 72 yr) with histologically confirmed adenocarcinoma of the prostate and a baseline PSA >2 ng/ml.
Results and limitations: At baseline, median serum testosterone was 4.13 ng/ml (range: P25–P75, 3.37–5.19 ng/ml) and PSA was 27.6 ng/ml (range: P25–P75, 11.9–55.0 ng/ml). On day 3, 88% and 92% of patients in the groups to whom 200-mg and 240-mg initial doses of degarelix were administered, respectively, had testosterone levels ≤0.5 ng/ml. For patients with testosterone levels ≤0.5 ng/ml at 1 mo, the testosterone levels remained ≤0.5 ng/ml until the end of the study in 100% of the patients treated with a monthly maintenance dosage of 160 mg of degarelix. No evidence of testosterone surge was detected. PSA decreased by 97–98% after 1 yr and the median time to 90% reduction in PSA was 8 wk in all but one patient (from the 80-mg dosage treatment group at the intial 200-mg dose of degarelix). Thirteen patients (6%) withdrew from the study due to adverse events, largely related to androgen deprivation.
Conclusions: Degarelix treatment for 1 yr resulted in a fast, profound, and sustained suppression of testosterone and PSA, with no evidence of testosterone surge. Degarelix was well tolerated.

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1. Introduction

Prostate cancer is a major cause of mortality and morbidity: In Europe, it is the most frequently diagnosed cancer in men (20.3% of the total cancer cases), followed by lung cancer and colorectal cancer [1].

Prostate cancer is androgen-dependent; androgen ablation remains the mainstay management approach towards advanced disease, with a well-recognised palliative effect. The gold-standard androgen-deprivation therapy is orchiectomy [2]. Surgical castration is, however, an irreversible procedure. A more reversible approach is pharmacological suppression of testosterone production or medical androgen deprivation.

The sequencing of the hypothalamic gonadotropin-releasing hormone (GnRH) was followed by the development of synthetic agonists with prolonged half-life and potency [3]. Chronic GnRH-agonist administration results in suppression of luteinising hormone (LH) from the anterior pituitary gland and, consequently, results in an inhibition of testosterone secretion through a down-regulation of the GnRH receptors in the pituitary [4–6]. However, the GnRH agonists initially activate the receptors, resulting in a surge in LH and testosterone as well as a delayed reduction in prostate-specific antigen (PSA) levels for 2–3 wk before androgen deprivation is achieved [7,8]. The surge can delay the therapeutic benefit and may exacerbate the clinical status by provoking or exacerbating symptoms such as urinary retention, bone pain, and paraplegia due to spinal-cord compression by spinal metastases [9]. Patients most at risk for this clinical flare are those with high-volume, symptomatic, metastatic disease [10]. Intermittent use of hormonal therapy includes periods without testosterone suppression. In the absence of robust, controlled, clinical trial data, this approach should be considered experimental. In the search for more effective therapies, GnRH blockers have been developed that suppress the release of gonadotropins by binding to pituitary GnRH receptors. GnRH blockers do not induce a testosterone surge but work by immediately suppressing the release of gonadotropins and testosterone.

Degarelix is a novel GnRH-receptor blocker with weak histamine-releasing properties and more rapid and profound testosterone suppression compared to existing GnRH antagonists [11–15]. When administered subcutaneously it immediately blocks GnRH receptors in the pituitary, resulting in a fast and sustained suppression of gonadotropin secretion without the initial stimulation of the gonadotropic axis [11].

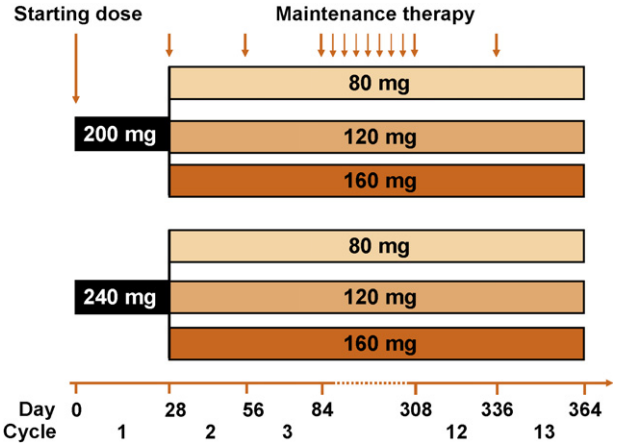

Fig. 1 – Study design. A total of 180 patients were to be enrolled for a study period of 13 28-d treatment cycles made up of one injection of an initial dose (200 mg or 240 mg of degarelix) and 12 monthly injections of a maintenance dose (80 mg, 120 mg, or 160 mg of degarelix).

The main objective of the present study was to investigate different treatment regimens of degarelix in the treatment of prostate cancer.

2. Methods

2.1. *Study design*

This was an open-label, randomised, parallel-group, dosage-finding study whose plan was to randomise a total of 180 patients into six treatment groups. Patients were enrolled for a period of 13 treatment cycles (each cycle was 28 d long) to receive one initial dose (200 mg or 240 mg of degarelix) and 12 doses of monthly maintenance therapy (80 mg, 120 mg, or 160 mg of degarelix; Fig. 1). Degarelix was supplied as a freeze-dried powder for suspension in water. The concentration of degarelix in the injection suspension was 40 mg/ml. Injections were given subcutaneously (initially two injections of 3-ml degarelix suspension, then one 2–4-ml injection per month [depending on group]) in predefined areas on the abdomen.

2.2. *Patients*

Male patients ≥18 yr of age and with histologically confirmed adenocarcinoma of the prostate (all stages), in whom endocrine treatment (except for neoadjuvant hormonal therapy) was indicated, were included. The patients had to have a baseline serum testosterone concentration above the lower limit of normal range in elderly men (defined as 2.2 ng/ml), an Eastern Co-operative Oncology Group score of ≤2, a PSA level of ≥2 ng/ml, a bone scan, and a current TNM classification staging (including bone scan) within 3 mo prior to the study. Previous or current hormonal management of prostate cancer was not allowed except in patients who had undergone curative-intent prostatectomy or radiotherapy in which neoadjuvant or adjuvant hormonal therapy for a maximum

of 6 mo was accepted (discontinued >12 mo prior to inclusion in this study). The patients were not allowed to be treated with any other testosterone-modifying drugs. Patients that were considered to be candidates for curative therapy as judged by the investigators were excluded. The patient's participation was discontinued if they had an inadequate testosterone suppression (defined as testosterone >1.0 ng/ml at one measurement or >0.5 ng/ml at two consecutive measurements from 1 mo and onwards).

2.3. Assessments

The study was performed in accord with the Declaration of Helsinki and its amendments [16]. Independent ethics committees of the participating centres approved the study. The patients were given oral and written information about the study, and they provided written consent to participate before any study-related activities were performed.

The primary end point of the study was to determine the proportion of patients with serum testosterone ≤0.5 ng/ml at 1 mo and at every monthly visit up to 1 yr. Secondary end points were included: the proportion of patients with testosterone ≤0.5 ng/ml up to 1 yr for those patients with testosterone ≤0.5 ng/ml at the 1-mo assessment; the proportion of patients with a testosterone level ≤0.5 ng/ml at day 3; times to reach 50% and 90% reduction in PSA; time to reach PSA progression (defined as a PSA increase ≥50% and at least 5 ng/ml compared to nadir on two consecutive visits at least 2 wk apart), and pharmacodynamic parameters (serum testosterone, dihydrotestosterone [DHT], PSA, LH, and follicle-stimulating hormone [FSH]) over time. When planning the study, the intent was to primarily analyse the data after 6 mo; but in the course of conducting the study, it was decided that analysis of efficacy after 1 yr would be of greater interest.

Syngenta Central Toxicology Laboratories (York Bioanalytical Solutions and York Pivotal Laboratories) performed the serum testosterone measurements according to Good Laboratory Practice, using validated methods for detection of testosterone levels in the low range.

Safety assessments included laboratory parameters (biochemistry, haematology, and urinalysis) and clinical safety parameters (local tolerability, adverse events [AEs], electrocardiograms [ECGs], physical examination, vital signs, and body weight).

2.4. Statistics

The primary analysis was performed among ''completers'' (defined as patients who either attended the last visit or had at least one testosterone measurement >0.5 ng/ml between 1 mo and 1 yr) in the intention-to-treat (ITT) analysis set. The proportion of patients with suppressed testosterone was analysed by logistic regression, with initial dose, monthly maintenance dosage, and the interaction as variables.

With a sample size of 180 patients, it would be possible to detect a difference in the proportion of patients with serum testosterone levels ≤0.5 ng/ml between two maintenance dosages of 95% versus 75% with a power of 80% based on a two-sided chi-squared test with continuity correction and a 5% significance level.

3. Results

3.1. Patient flow

Some 216 patients were screened; 189 were randomised into treatment (= all-patient randomised analysis set), and 187 patients received study medication (= ITT analysis/safety analysis set; Fig. 2). Four patients violated at least one of the predefined criteria for major protocol deviation (two patients received the wrong dosage, one did not fulfil the inclusion criterion of histologically confirmed adenocarcinoma, and one had had cancer disease during the previous 5 yr [exclusion criterion]) and were therefore excluded from the per-protocol (PP) analysis set. Sixteen patients (8.5%) were withdrawn due to inadequate testosterone suppression; 13 (6.9%) were withdrawn due to AEs; and 13 (6.9%) were withdrawn due to ''other reasons''—including withdrawal of consent (7 patients), noncompliance with the study protocol (2 patients), loss to follow-up (2 patients), PSA progression (1 patient), and exclusion criteria fulfilled after randomisation (1 patient).

3.2. Demographics and baseline characteristics

The median testosterone and PSA levels at baseline were 4.13 ng/ml (range: P25–P75, 3.37–5.19 ng/ml) and 27.6 ng/ml (range: P25–P75, 11.9–55.0 ng/ml), respectively (Table 1). There were no differences between the six treatment groups with respect to demographics and baseline characteristics except for the median PSA. The 200/80 treatment group (initial dose of 200 mg of degalarix followed by monthly maintenance dosage of 80 mg of degarelix) had a median baseline PSA of 15.2 ng/ml, while the 240/120 treatment group (initial dose of 240 mg of degalarix followed by monthly maintenance dosage of 120 mg of degarelix) had a median PSA of 35.3 ng/ml.

3.3. Testosterone and dihydrotestosterone levels

Suppression of serum testosterone levels (Fig. 3) was fast. On day 3, 88% and 92% of patients in the initial-dosage groups of 200-mg and 240-mg of degarelix, respectively, showed testosterone levels ≤0.5 ng/ml. After 1 mo, testosterone levels were ≤0.5 ng/ml in 86% (81/94) and 95% (87/92) of patients initially treated with 200 mg and 240 mg of degarelix, respectively. The between-group difference (odds ratio 2.57, 95% CI, 1.010–6.651, $P = 0.048$) was statistically significant.

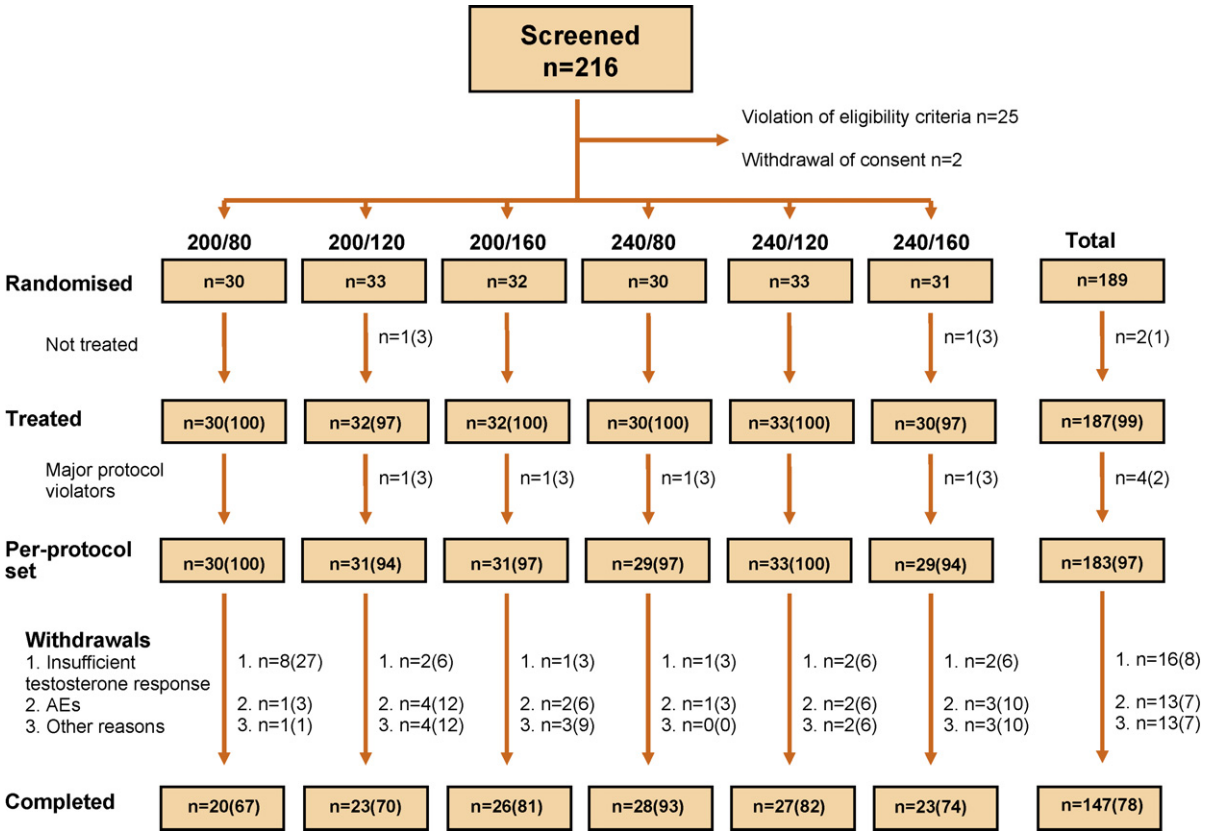

Fig. 2 – Patient flow. Numbers in parentheses denote the percentage of randomised patients of that treatment group. Insufficient testosterone response was defined as one testosterone value >1.0 ng/ml or two consecutive values >0.5 ng/ml after 1 mo of treatment and onwards.

Serum testosterone was maintained at very low levels throughout the study in all treatment groups (Fig. 4A). For the 147 patients with testosterone levels ≤0.5 ng/ml at the end of the study, the median testosterone level was 0.121 ng/ml (P25–P75 0.077–0.167 ng/ml). The proportion of patients divided into the two initial dosage and three monthly maintenance dosage treatment groups, with testosterone ≤0.5 ng/ml from 1 mo to the end of the study, can be seen in Table 2A. The patients with testosterone levels ≤0.5 ng/ml at 1 mo were pooled into groups of different maintenance doses, irrespective of initial dose (Table 2B). For patients with testosterone levels ≤0.5 ng/ml at 1 mo, the testosterone levels remained ≤0.5 ng/ml until the end of the study in 92%, 96%, and 100% of the patients treated with monthly maintenance dosages of 80 mg, 120 mg, and 160 mg of degarelix, respectively.

The reductions in DHT and FSH levels were similar in all treatment groups (Fig. 3). The median reductions in DHT and FSH levels at the end of the study ranged from 83% to 90% and 74% to 88%, respectively.

3.4. *PSA and other assessments*

The median time to reach a 50% reduction in PSA was 14 d for all groups (Fig. 3 and Table 3). The median time to reach a 90% reduction in PSA was 56 d for all groups except for the 200/80 group (84 d). Serum PSA was maintained at very low levels throughout the study for all groups (Fig. 4B). The percentages of patients reaching PSA levels ≤4 ng/ml and ≤0.4 ng/ml after 6 mo are shown in Table 3. After 12 mo, the median reduction in PSA compared to baseline was 97–98%. There were 14 patients (7%) with PSA progression (Table 3).

There was a rapid decrease in LH levels (Fig. 3), and 1 d after receiving the initial doses of degarelix, the median reduction was ≥80% in all treatment groups. At the end of the study, the median reduction in LH compared to baseline was 92–95%. One day after the initial dose of degarelix, the median decrease in FSH levels compared to baseline ranged from 36% to 39%. At the end of the study, the median reduction in FSH compared to baseline was 76–88%.

Table 1 – Patient demographics and baseline characteristics

	Initial dose of degarelix (mg)/monthly maintenance dosage of degarelix (mg)						
	200/80	200/120	200/160	240/80	240/120	240/160	Total
ITT analysis set	30	32	32	30	33	30	187
Age (yr)							
Median (range)	71 (55–86)	69 (55–93)	74 (58–84)	70 (57–88)	71 (56–88)	73 (52–82)	72 (52–93)
Race, N (%)							
Asian					1 (3)		1 (<1)
Black or African heritage	1 (3)	2 (6)	1 (3)		2 (6)		6 (3)
White	29 (97)	30 (94)	31 (97)	30 (100)	30 (91)	30 (100)	180 (96)
BMI (kg/m^2)							
Median (range)	26 (18–36)	26 (20–37)	25 (18–36)	26 (18–41)	25 (18–33)	25 (20–30)	26 (18–41)
Weight (kg)							
Median (range)	80 (50–109)	77 (52–111)	74 (58–126)	79 (56–150)	80 (50–106)	74 (62–104)	77 (50–150)
Testosterone (ng/ml)							
Median (P25–P75)	4.47 (3.58–5.49)	3.93 (2.65–4.48)	4.79 (3.64–5.53)	4.28 (2.74–5.43)	4.07 (3.27–4.84)	3.88 (3.37–4.80)	4.13 (3.37–5.19)
PSA (ng/ml)							
Median (P25–P75)	15.2 (7.3–36)	31.5 (18–98)	31.5 (15–67)	23.1 (11–52)	35.3 (14–55)	32 (11–73)	27.6 (12–55)
Stage of disease, N (%)							
Localised	8 (27)	6 (19)	6 (19)	5 (17)	11 (33)	5 (17)	41 (22)
Locally advanced	8 (27)	11 (34)	11 (34)	12 (40)	8 (24)	10 (33)	60 (32)
Metastatic	4 (13)	8 (25)	5 (16)	5 (17)	7 (21)	7 (23)	36 (19)
Not classifiable	10 (33)	7 (22)	10 (31)	8 (27)	7 (21)	8 (27)	50 (27)
Gleason grade, N (%)							
2–4	4 (13)	10 (31)	6 (19)	9 (30)	4 (12)	3 (10)	36 (19)
5–6	13 (43)	10 (31)	14 (44)	10 (33)	17 (52)	12 (40)	76 (41)
7–10	13 (43)	12 (38)	10 (31)	11 (37)	12 (36)	15 (50)	73 (39)

ITT, intention to treat; N, number of patients in the analysis set; BMI, body mass index; PSA, prostate-specific antigen.

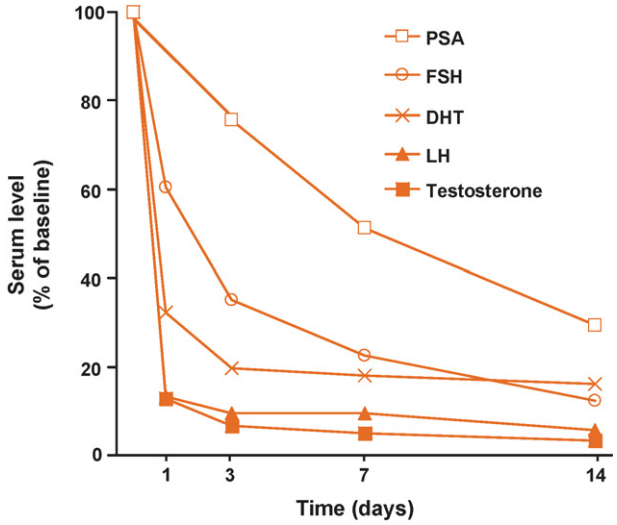

Fig. 3 – Changes from baseline in testosterone, prostate-specific antigen (PSA), luteinising hormone (LH), dihydrotestosterone (DHT), and follicle-stimulating hormone (FSH) in the group that received an initial dose of 240 mg of degarelix during the first 14 d. Baseline values: testosterone 4.07 ng/ml; PSA 31.8 ng/ml; LH 5.30 IU/l; DHT 340 pg/ml; FSH 8.85 IU/l.

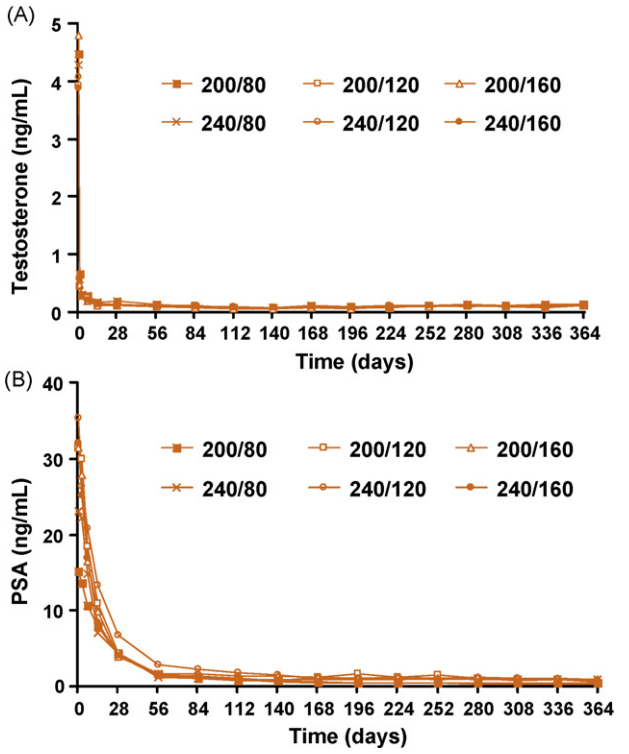

Fig. 4 – Serum (A) testosterone and (B) prostate-specific antigen levels (ng/ml) during the study in the six treatment groups.

3.5. *Safety*

The most frequently reported AEs were related to androgen deprivation. AEs included hot flushes (33%), injection-site pain (10%), increased body weight (9%), back pain, fatigue and urinary tract infection (6% each) and increased serum alanine aminotransferase (ALT) levels, cough, and diarrhoea (5% each; Table 4). There were no cases of systemic allergic reactions. Most of the AEs were mild to moderate in intensity; 11% of patients experienced at least one severe AE. Of the 18 patients with injection site pain, 11 had pain of mild intensity, and 8 had pain of moderate intensity; one patient reported both mild and moderately intense pain. No injection-site AE was considered to be severe. There were 27 patients (14%) who experienced serious treatment-emergent AEs. One patient had a serious AE which was evaluated to be possibly related to degarelix by the investigator: a 65-yr-old man who was hospitalised for depression. Thirteen patients (7%) withdrew from the study due to AEs (Fig. 2): three with disease progression, three with

Table 2 – Proportion of patients with serum testosterone levels ≤0.5 ng/ml at all monthly visits from 1 mo to 12 mo (A) in all treatment groups and (B) in the monthly maintenance doses for those patients with serum testosterone levels ≤0.5 ng/ml at 1 mo

	Monthly maintenance dosage of degarelix (mg)											
	80				120				160			
Initial dose (mg)	*N*	*n*	%	95% CI	*N*	*n*	%	95% CI	*N*	*n*	%	95% CI
A												
200	28	17	61	41–78%	25	21	84	64–95%	27	26	96	81–100%
240	30	27	90	73–98%	30	27	90	73–98%	25	23	92	74–99%
B												
Both initial doses (patients with testosterone ≤0.5 ng/ml at 1 mo)	48	44	92	80–98%	50	48	96	86–100%	49	49	100	92–100%

N, number of patients in the analysis set; *n*, number of patients with all testosterone measurements ≤0.5 ng/ml at all measuring points from 1 mo to 12 mo; %, $n/N \times 100$. 95% CI (confidence interval) was calculated by Clopper-Pearson method.

Table 3 – Time to reach 50% and 90% reduction in prostate-specific antigen (PSA), time to PSA progression, and percentage of patients reaching PSA levels ≤4 ng/ml and ≤0.4 ng/ml after 6 mo of treatment

	Initial dose of degarelix (mg)/monthly maintenance dosage of degarelix (mg)					
	200/80	200/120	200/160	240/80	240/120	240/160
ITT analysis set	30	32	32	30	33	30
Time to 50% reduction (d)						
N	28	31	32	30	33	27
Median (range)	14 (7–224)	14 (3–84)	14 (3–42)	14 (3–56)	14 (3–84)	14 (3–56)
Life table estimates						
Median (95% CI)	14 (14–28)	14 (14–14)	14 (7–14)	14 (14–14)	14 (14–14)	14 (7–14)
Log-rank test	0.0933					
Time to 90% reduction (d)						
N	20	25	29	24	24	26
Median	56 (28–168)	56 (14–336)	56 (14–336)	56 (14–196)	56 (28–364)	56 (14–196)
Life table estimates						
Median (95% CI)	84 (56–168)	56 (56–112)	56 (56–56)	56 (56–56)	56 (56–224)	56 (28–84)
Log-rank test	0.165					
Time to progression (d)						
N		3	1	4	4	2
Median		224 (140–308)	308 (308–308)	280 (252–336)	224 (126–364)	140 (140–140)
Log-rank test	0.429					
Patients achieving threshold levels after 6 mo (%)						
PSA ≤4 ng/ml	95	69	89	82	77	82
PSA ≤0.4 ng/ml	48	31	36	41	28	48

ITT, intention to treat; *N*, number of patients in the analysis set; CI, confidence interval.

cardiovascular events, two with cerebrovascular accidents, two with cachexia, one with elevated liver enzymes, one with bronchopneumonia, and one with laryngeal cancer. With the exception of one patient (with disease progression), these AEs were serious, and none were assessed to be related to degarelix.

Eleven patients (6%) died during the study; none of these deaths were considered to be related to degarelix. There was no temporal correlation between administration of degarelix and occurrence of death, and no pattern of the causes of deaths could be observed. Two deaths were caused by myocardial infarction: A 93-yr-old man with no history of cardiovascular disease died 17 d after receiving the second dose of degarelix, and an 80-yr-old patient with history of heart disease died 1 wk after receiving the first dose of degarelix. One 68-yr-old man with a history of heart disease had symptoms of angina pectoris 24 d after his third dose of degarelix and was admitted to hospital, where cardiac failure developed, and the patient

Table 4 – Incidence of treatment-emergent adverse events (incidence of ≥5% in the total number of patients)

	Initial dose of degarelix (mg)/monthly maintenance dosage of degarelix (mg)						
	200/80	200/120	200/160	240/80	240/120	240/160	Total
ITT analysis set	30	32	32	30	33	30	187
Any AE, *N* (%)	17 (57)	21 (66)	24 (75)	19 (63)	24 (73)	20 (67)	125 (67)
Hot flush	14 (47)	8 (25)	10 (31)	11 (37)	9 (27)	10 (33)	62 (33)
Injection-site pain	1 (3)	3 (9)		6 (19)	6 (18)	2 (7)	18 (10)
Weight increase		3 (9)	4 (13)	4 (13)	3 (9)	2 (7)	16 (9)
Back pain	2 (7)	3 (9)	2 (6)	1 (3)	2 (6)	1 (3)	11 (6)
Fatigue	2 (7)	1 (3)	2 (6)	3 (10)	1 (3)	2 (7)	11 (6)
Urinary tract infection	2 (7)	2 (6)	2 (6)	2 (7)	2 (6)	1 (3)	11 (6)
ALT increase	3 (10)	1 (3)	3 (9)		1 (3)	1 (3)	9 (5)
Cough	2 (7)	1 (3)	2 (6)	1 (3)		3 (10)	9 (5)
Diarrhoea	1 (3)	3 (9)	2 (6)		1 (3)	2 (7)	9 (5)

ITT, intention to treat; AE, adverse events; *N*, number of subjects with adverse events; ALT, alanine aminotransferase.

died. Eight other patients died: three of disease progression, two of cachexia, one of bronchopneumonia, one of larynx carcinoma, and one of cerebrovascular accident.

Three patients had increased blood urea, and two had increased serum creatinine levels. The liver function tests were evaluated with guidance from the Food and Drug Administration Clinical White Paper for the detection of drugs with serious hepatotoxicity [17]. There were 10 patients (5%) with ALT levels $>3 \times$ the upper limit of normal range (ULN), but none of these patients had an increase in bilirubin $>1.5 \times$ ULN. These elevations were reversible during continued treatment, and there was no obvious relation between the proportion of patients with elevated ALT levels and patient dose of degarelix.

4. Discussion

The purpose of the present study was to investigate different regimens of degarelix in the treatment of prostate cancer. For this, subcutaneous injections of a initial dosage of either 200-mg or 240-mg, 1-mo depot degarelix followed by monthly maintenance dosage of 80 mg, 120 mg, or 160 mg of degarelix for 12 mo were investigated.

By day 3, 90% of the patients in both treatment groups showed serum testosterone levels of $\leq$0.5 ng/ml. After 1 mo, a higher proportion of patients had $\leq$0.5 ng/ml after the initial 240-mg dose of degarelix (95%) than after the initial 200 mg dose (88%). This suggests that 240 mg of degarelix is a suitable initial dosage. Furthermore, at the end of the study there was a higher proportion of patients with serum testosterone levels $\leq$0.5 ng/ml in the group that received monthly maintenance doses of 160 mg of degarelix than in the 80-mg dosage group. Thus, 160 mg (40 mg/ml) administered every 4 wk seems to be an appropriate maintenance dosage to provide long-term testosterone suppression, and this dosage is being evaluated further in the degarelix development programme.

PSA levels were also rapidly reduced following initiation of degarelix treatment, in contrast to GnRH agonists, where delays in the decrease of serum PSA levels have been noted for up to 3 wk [6,7]. Degarelix represents a new mechanism of action for androgen deprivation therapy, with the ability to induce rapid reduction of testosterone and PSA and thus avoiding the use of antiandrogen flare protection.

Degarelix administered for 1 yr was well tolerated. The AEs reported were mostly related to hormonal androgen deprivation, and no dose-dependent side-effects were detected. The causes and incidence of deaths (6%) during the study are in line with what can be expected in a patient population of this age, and this rate is comparable to the mortality that has been reported in previous androgen-deprivation studies in similar patient populations [18,19].

Rapid testosterone suppression without testosterone surge has previously been observed with the GnRH antagonist abarelix [20,21]. However, abarelix treatment was shown to induce immediate-onset systemic allergic reactions in a low proportion of patients [21].

5. Conclusions

Results from this dosage-finding study suggest a preferred initial dose to be 240 mg of degarelix, which had an immediate onset of action and induced rapid testosterone suppression to effective androgen-deprivation levels ($\leq$0.5 ng/ml) in $>$90% of patients within 3 d. No testosterone surges were observed. Subsequent monthly injections, at a preferred dosage of 160 mg degarelix for 1 yr, resulted in profound and sustained suppression of testosterone and PSA. Degarelix was well tolerated, with no evidence of systemic allergic reactions. Degarelix represents a new pharmacological approach in the hormonal treatment of prostate cancer, with effects on testosterone and PSA that are similar to orchiectomy.

Author contributions: Hendrik Van Poppel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Van Poppel, Tombal, de la Rosette, Persson, Jensen, and Olesen
Acquisition of data: Van Poppel, Tombal, de la Rosette, Persson, Jensen, and Olesen
Analysis and interpretation of data: Van Poppel, Tombal, de la Rosette, Persson, Jensen, and Olesen
Drafting of the manuscript: Van Poppel, Tombal, de la Rosette, Persson, Jensen, and Olesen
Critical revision of the manuscript for important intellectual content: Van Poppel, Tombal, de la Rosette, Persson, Jensen, and Olesen
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Editorial Comment on: Degarelix: a Novel Gonadotropin-Releasing Hormone (GnRH) Receptor Blocker—Results from a 1-yr, Multicentre, Randomised, Phase 2 Dose-Finding Study in the Treatment of Prostate Cancer

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The Nobel prize-winning discovery of the importance of androgenic influences on the growth of prostate cells by Charles B. Huggins and C.V. Hodges in 1941 established androgen-deprivation therapy (ADT) as a treatment for metastatic prostate cancer. As known from the literature, androgen-deprivation therapy reduces bone pain in 80–90% of cases, leads to objective responses in soft tissue and bone, and normalizes serum prostate-specific antigen (PSA) in over 90% of patients [1,4,5].

However, ADT results in erectile dysfunction, loss of libido, fatigue, hot flashes, and loss of muscle and bone mass, all of which adversely impact quality of life.

Various forms of ADT exist today, including bilateral orchiectomy, GnRH agonists, estrogen therapy, ketokonazole to block adrenal androgens, and combined androgen blockage, where a GnRH agonist or orchiectomy is combined with an antiandrogen.

The study of van Poppel et al describes a multicentre, randomised phase 2 dose-finding trial of the novel GnRH antagonist degarelix [2]. A faster and more profound testosterone suppression can be achieved using this novel agent compared to other GnRH antagonists.

The authors defined the castration levels as $\leq$50 ng/dl. Due to novel, more sensitive assays — such as the radioimmunoassay technique and the chemiluminescent technique—levels as low as 20 ng/dl can be detected. There is limited clinical basis for reducing castrate levels, and no studies have shown that by lowering the level of testosterone to $\leq$20 ng/dl survival is statistically improved. It would be interesting to see what the response rate in this lower castration level group may be.

However, it must be recognized that 2–13% of patients fail to achieve $<$50 ng/dl testosterone following LHRH therapy and 13–37% fail to reach $<$20 ng/dl [3].

Another interesting point that warrants discussion is the rate of withdrawals. Fifteen percent of the enrolled patients withdrew due to adverse events or insufficient castration level. This level seems very high and needs additional corroboration.

Nevertheless, this is an interesting and important study to mark the emerging role of GnRH antagonists in the treatment of prostate cancer.

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Editorial Comment on: Degarelix: A Novel Gonadotropin-Releasing Hormone (GnRH) Receptor Blocker—Results from a 1-yr, Multicentre, Randomised, Phase 2 Dose-Finding Study in the Treatment of Prostate Cancer

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This study by Van Poppel et al [1] looks at the results of a phase II study of toxicity and efficacy, combined with the dose-ranging estimation, of the new compound degarelix. The study sought to assess patients for two separate loading doses of the compound, and three maintenance doses given over 12 mo. The study used as its surrogate testosterone and prostate-specific antigen (PSA).

Degarelix is not the first type of antagonist whose perceived benefit is the lack of testosterone flare (as shown by references 18 and 20 in the original trial). An earlier compound, Abarelix, was withdrawn (reference 21) because of toxicity problems due to hypersensitivity [2–5].

In essence, this is a chemical castration and appears to confer no greater benefit to the patient than an orchiectomy. Its only rationale, as an agent in intermittent hormone treatment, is somewhat lightly dismissed by the authors of the study. There is no data supporting it as an agent if recommended for continuous usage, and the long-term efficacy as compared with LRHR agonists is not yet in hand. In the initial 12 mo of this phase II study, very few, if any, problems in toxicity were apparent. But there has not yet been sufficient patient time to demonstrate possible longer-term toxicities. The fundamental question about an agent of this nature—which does not seek to demonstrate a significant advance in treatment efficiency or effectiveness—is: *cui bono*?

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