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The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer

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OBJECTIVE

To evaluate the efficacy and safety of degarelix, a new gonadotrophin-releasing hormone (GnRH) antagonist (blocker), vs leuprolide for achieving and maintaining testosterone suppression in a 1-year phase III trial involving patients with prostate cancer.

PATIENTS AND METHODS

In all, 610 patients with adenocarcinoma of the prostate (any stage; median age 72 years; median testosterone 3.93 ng/mL, median prostate-specific antigen, PSA, level 19.0 ng/mL) were randomized and received study treatment. Androgen-deprivation therapy was indicated (neoadjuvant hormonal treatment was excluded) according to the investigator's assessment. Three dosing regimens were evaluated: a starting dose of 240 mg of degarelix subcutaneous (s.c.) for 1 month, followed by s.c. maintenance doses of 80 mg or 160 mg monthly, or intramuscular (i.m.) leuprolide doses of 7.5 mg monthly. Therapy was maintained for the 12-month study. Both

the intent-to-treat (ITT) and per protocol populations were analysed.

RESULTS

The primary endpoint of the trial was suppression of testosterone to ≤ 0.5 ng/mL at all monthly measurements from day 28 to day 364, thus defining the treatment response. This was achieved by 97.2%, 98.3% and 96.4% of patients in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively (ITT population). At 3 days after starting treatment, testosterone levels were ≤ 0.5 ng/mL in 96.1% and 95.5% of patients in the degarelix 240/80 mg and 240/160 mg groups, respectively, and in none in the leuprolide group. The median PSA levels at 14 and 28 days were significantly lower in the degarelix groups than in the leuprolide group ($P < 0.001$). The hormonal side-effect profiles of the three treatment groups were similar to previously reported effects for androgen-deprivation therapy. The s.c. degarelix injection was associated with a higher rate of injection-site reactions than with the i.m. leuprolide injection (40% vs <1%; $P < 0.001$, respectively). There were additional differences between the degarelix and leuprolide groups for urinary tract infections

(3% vs 9%, $P < 0.01$, respectively), arthralgia (4% vs 9%, $P < 0.05$, respectively) and chills (4% vs 0%, $P < 0.01$, respectively). There were no systemic allergic reactions.

CONCLUSIONS

Degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1-year treatment period. Degarelix induced testosterone and PSA suppression significantly faster than leuprolide; PSA suppression was also maintained throughout the study. Degarelix represents an effective therapy for inducing and maintaining androgen deprivation for up to 1 year in patients with prostate cancer, and has a different mechanism of action from traditional GnRH agonists. Its immediate onset of action achieves a more rapid suppression of testosterone and PSA than leuprolide. Furthermore, there is no need for antiandrogen supplements to prevent the possibility of clinical 'flare'.

KEYWORDS

adenocarcinoma, prostate neoplasm, gonadotrophin-releasing hormone, prostate-specific antigen, testosterone

INTRODUCTION

Androgen-deprivation therapy (ADT) is commonly used in the management of advanced prostate cancer, as $\approx 80\%$ of patients with prostate cancer in whom

localized therapy fails are responsive to ADT [1]. AD can be achieved through bilateral orchidectomy or by administration of LHRH receptor agonists, the latter achieving the desired therapeutic goal (serum testosterone levels of ≤ 0.5 ng/mL) in 90–100% of patients,

but only after 7–21 days [2,3]. Moreover, the initial physiological response to LHRH agonist administration results in a supra-physiological increase in testosterone levels, also known as a biochemical surge, which might stimulate prostate cancer cells and lead

to an exacerbation of clinical symptoms such as spinal cord compression, bone pain and urethral obstruction (termed 'flare') [4–6]. Antiandrogens can be administered to mitigate the symptoms of clinical flare [7]. There are potential side-effects and cost issues associated with antiandrogens [8]. Renewed injections of LHRH agonist therapy are reported to also induce repeated increases in testosterone concentration [9].

The GnRH antagonist is a new class of agent that immediately blocks the GnRH receptor and thus produces rapid AD without the ensuing testosterone surge. Several GnRH antagonists have been investigated for treating prostate cancer, but many of these compounds have shown histamine-releasing properties, a lack of sustained efficacy, and/or solubility limitations that affect their clinical usefulness or even preclude their further development as clinically useful drugs [10]. The GnRH antagonist abarelix, was able to maintain medical castration (serum testosterone level < 0.5 ng/mL) in only 62–71% of patients after 1 year of therapy [11].

Degarelix, a new GnRH receptor blocker (antagonist), has been developed as a novel therapy for patients with prostate cancer who need ADT. Degarelix binds to and blocks the GnRH receptors in the anterior pituitary gland, resulting in decreased secretion of both LH and FSH. This leads directly to a rapid decrease in the production of testosterone. Testosterone suppression to castrate levels (≤ 0.5 ng/mL) [12] is achieved within 1–3 days of administration. In two recent phase II dose-finding clinical trials, a starting dose of 240 mg degarelix and maintenance doses of 80 or 160 mg were shown to effectively suppress testosterone levels in patients with prostate cancer, with no evidence of testosterone surge or induction of clinical flare [13,14]. To date, >2000 patients have participated in the degarelix clinical development programme. There have been no signs of immediate- or late-onset systemic allergic reactions with degarelix [13,14], in contrast to previously reported trials of other GnRH antagonists [15].

The objective of the present trial was to evaluate the efficacy and safety of two doses of degarelix vs a standard 7.5 mg dose of the LHRH agonist leuprolide (Lupron Depot®; TAP Pharmaceuticals Inc., USA). The trial was designed to show that degarelix was not

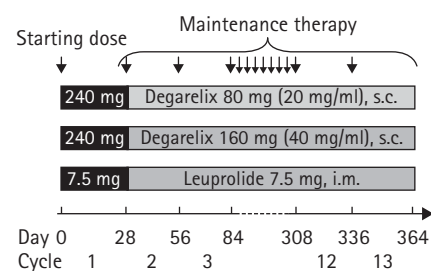
inferior to leuprolide for achieving and maintaining testosterone suppression (≤ 0.5 ng/mL) for 1 year.

PATIENTS AND METHODS

This was a three-armed, randomized (1:1:1), active-controlled, open-labelled, parallel-group phase III trial of 12 months' duration. Randomization lists were prepared centrally by the Department of Biometrics, Ferring Pharmaceuticals A/S, using a validated computer program. Randomization was stratified by geographical region and body weight. Sponsor personnel were unaware of the serum testosterone, PSA, LH and FSH results. In all, 610 patients were randomized and received either a degarelix s.c. starting dose of 240 mg (given as two \times 3 mL injections) and thereafter 12 monthly (every 28 days) maintenance doses of 80 mg (one 4 mL injection of 20 mg/mL; 207 men) or 160 mg (40 mg/mL; 202 men), or 12-monthly (every 28 days) i.m. injections of leuprolide 7.5 mg (given as one injection of ≈ 1 mL; TAP Pharmaceuticals; 201 men) (Fig. 1). In the leuprolide group, bicalutamide (50 mg tablet, once daily) could be administered at the start of treatment for clinical flare protection at the discretion of the investigator. Degarelix was supplied as a freeze-dried powder for suspension in water. Injections were given s.c. in predefined areas on the abdomen. Leuprolide was supplied in a pre-filled dual-chamber syringe and was administered after reconstitution as an i.m. injection according to the directions for use as per the manufacturer's labelling.

Men aged ≥ 18 years with histologically confirmed adenocarcinoma of the prostate (all stages), for whom endocrine treatment was indicated (except for neoadjuvant hormonal therapy), were recruited. The population included patients with an increasing PSA level after treatment with curative intent, i.e. those with biochemical failure and those with metastatic disease (hormone-sensitive). Patients were required to have a screening serum testosterone level of >1.5 ng/mL, an Eastern Cooperative Oncology Group score of ≤ 2 , and a PSA level of ≥ 2 ng/mL. Previous or current hormonal management of prostate cancer was not allowed, except in patients having undergone localized therapy of curative intent in which neoadjuvant or adjuvant hormonal therapy for ≤ 6 months was

FIG. 1. The study design; 600 patients were to be enrolled for a study period of 13 treatments in 28-day cycles, made up of either a starting dose of degarelix s.c. 240 mg and thereafter monthly maintenance doses of 80 mg (20 mg/mL) or 160 mg (40 mg/mL), or monthly i.m. injections of leuprolide 7.5 mg.



accepted (discontinued >6 months before inclusion). Patients considered to be candidates for curative therapy were excluded.

The trial was conducted in accordance with the Declaration of Helsinki as well as Good Clinical Practice Guidelines [16]. Appropriate independent ethics committees and institutional review boards for the participating sites were used throughout the trial. Central laboratories were used to measure all serum hormone (testosterone, LH and FSH) and PSA samples. Serum testosterone levels were determined using a validated liquid chromatography system with tandem mass spectrometry assay. PSA was analysed using a validated immunoassay. LH and FSH were analysed using a validated immunochemiluminometric method.

Safety and tolerability assessments included laboratory values (biochemistry, haematology and urine analysis), clinical variables (injection-site tolerability, adverse events, AEs, electrocardiograms, a physical examination, vital signs, and body weight). Global Central Laboratories PPD (Wilmington, NC, USA) analysed all clinical chemistry, haematology and urine analysis variables.

All endpoints included in the study are shown in Table 1; constraints on space preclude the reporting of all study endpoints; those omitted from the current report are highlighted in Table 1. The primary endpoint was suppression of testosterone level to ≤ 0.5 ng/mL between 28 and 364 days, which was considered a treatment response. The effectiveness of degarelix was determined by showing that: (i) The lower limit of the 95% CI

TABLE 1 Endpoints of the study; those marked with * were not presented in this report

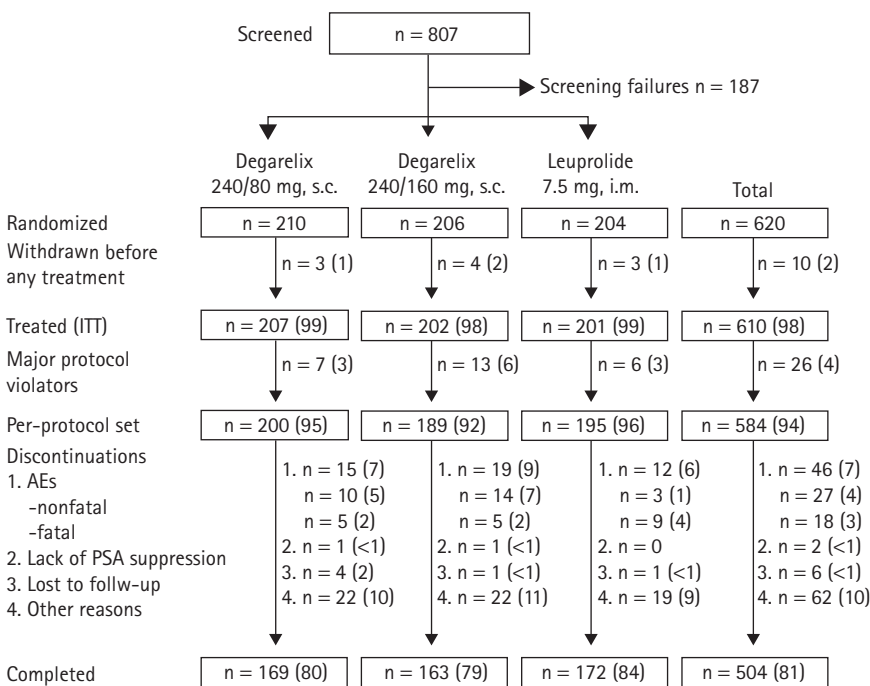
Endpoint	Detail
Primary	Cumulative probability of testosterone ≤ 0.5 ng/mL at any monthly measurement from 28 to 364 days
Secondary	Proportion of patients with testosterone surge during the first 2 weeks of treatment
	Proportion of patients with testosterone level ≤ 0.5 ng/mL at day 3
	Probability of testosterone ≤ 0.5 ng/mL from 56–364 days
	Probability of sufficient testosterone response from 28–364 days
	Frequency and size of testosterone increases at 255 days and/or 259 vs testosterone level at 252 days
	Serum levels testosterone, LH, FSH and PSA over time
	Percentage change in PSA from baseline to 14–28 days
	Time to PSA failure (PSA increase $\geq 50\%$ from nadir and ≥ 5 ng/mL on two consecutive occasions at least 2 weeks apart)
	Degarelix concentration over the first month and trough levels at 308 and 336 days*
	Frequency and severity of AEs
	Clinically significant changes in laboratory values
	Change in electrocardiogram and vital signs
	Quality of life on 0, 28, 84, 168, and 364 days*
	Hot flush frequency and hot flush score daily from study start until 354 days*

The treatment response rate was based on the time to reach a testosterone level of ≤ 0.5 ng/mL from 28 to 364 days and was estimated by the Kaplan-Meier method. For each of the treatment groups, the response rate and 95% CI were calculated by log-log transformation of the survivor function. Differences between the groups were assessed using a 97.5% CI calculated by normal approximation using pooled standard error.

Assuming a common response rate of 96% and a common withdrawal rate of 15%, with a sample size of 200 patients per treatment group, it would be possible to detect, with 90% power, that the lower limit of the 95% CI was no lower than 90% (effectiveness criterion 1). With 200 patients per treatment group it was also possible to show that degarelix was not inferior to leuprolide (effectiveness criterion 2) with $>90\%$ power.

RESULTS

FIG. 2. Patient flow; numbers in parenthesis denote the percentage of randomized patients of that treatment group.



The study was conducted between February 2006 and October 2007. Of the 807 patients screened, 620 were randomized and 610 received study medication (Fig. 2). Of the entire study population, 26 patients (4%) violated at least one predefined criteria, constituting a major protocol deviation, and thus were excluded from the PP analysis set. In all, 116 (19%) randomized patients (20% degarelix and 16% leuprolide) discontinued the trial. The baseline characteristics and demographics were comparable across the treatment groups (Table 2).

Both degarelix dose regimens were able to maintain testosterone suppression, as the lower limit of the 95% CI of testosterone ≤ 0.5 ng/mL for degarelix was $\geq 90\%$ from 28 to 364 days (Table 3); furthermore degarelix was at least as effective as leuprolide at maintaining a treatment response from 28 days to the end of the study at 364 days (Fig. 3). A treatment response in the ITT population was achieved by 97.2%, 98.3% and 96.4% of patients in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively. For the PP population, corresponding values were 97.2%, 99.4% and 96.3%. In total, 15 patients had at least one testosterone value of >0.5 ng/mL (referred to as 'escapers') between 28 and 364 days. Of these escapers, five of 207 (2.4%) and three of 202 (1.5%) were in the degarelix 240/80 and 240/160 mg groups, respectively, and seven of 201 (3.5%) were in the leuprolide group. For

for the cumulative probability of testosterone being ≤ 0.5 ng/mL from 28 to 364 days for degarelix was $\geq 90\%$; (ii) degarelix was not inferior to leuprolide for the cumulative probability of testosterone levels being ≥ 0.5 ng/mL from 28 to 364 days. The non-

inferiority margin for the difference between treatments (degarelix vs leuprolide) was -10% . Each degarelix arm was compared separately with leuprolide, and endpoints were assessed in both the intent-to-treat (ITT) and per protocol (PP) populations.

TABLE 2 Patient demographics and baseline characteristics

Variable	Degarelix		Leuprolide 7.5 mg	Total
	240/80 mg	240/160 mg		
ITT analysis set, n	207	202	201	610
Median (range) age, years	72 (51–89)	72 (50–88)	74 (52–98)	73 (50–98)
Median (25–75 percentile) Testosterone, ng/mL	4.11 (3.05–5.32)	3.78 (2.86–5.05)	3.84 (2.91–5.01)	3.93 (2.89–5.10)
PSA, ng/mL	19.8 (9.4–46)	19.9 (8.2–68)	17.4 (8.4–56)	19.0 (8.7–57)
Stage of disease, n (%)				
Localized*	69 (33)	59 (29)	63 (31)	191 (31)
Locally advanced†	64 (31)	62 (31)	52 (26)	178 (29)
Metastatic	37 (18)	41 (20)	47 (23)	125 (20)
Not classifiable	37 (18)	40 (20)	39 (19)	116 (19)
Gleason grade, n (%)				
2–4	20 (10)	21 (11)	24 (12)	65 (11)
5–6	68 (33)	67 (34)	63 (32)	198 (33)
7	63 (30)	56 (28)	62 (31)	181 (30)
8–10	56 (27)	56 (28)	51 (26)	163 (27)

*Localized = T1/2, NX or NO, and M0; †Locally advanced = T3/4, NX or NO, and M0, or N1 and M0.

TABLE 3 Testosterone response rates (i.e. cumulative probability of a testosterone level of ≤ 0.5 ng/mL from 28 to 364 days: Kaplan-Meier estimates of individual response rates; ITT analysis set)

	n	n Responders	% (95% CI)
Degarelix 240/80 mg s.c.	207	202	97.2 (93.5–98.8)
Degarelix 240/160 mg s.c.	202	199	98.3 (94.8–99.4)
Leuprolide 7.5 mg i.m.	201	194	96.4 (92.5–98.2)

n, number of dosed patients; Responder, testosterone ≤ 0.5 ng/mL at 28–364 days; %, Kaplan-Meier estimated response rates.

each of the treatment groups, the lower bound of the two-sided 95% CI was above the 90% threshold, indicating that the predefined success criterion was met. For both degarelix groups the drug was not inferior to leuprolide. As a secondary endpoint, patients having one testosterone value of >1.0 ng/mL or two consecutive values of >0.5 ng/mL from 28 to 364 days were considered to have an insufficient response to treatment. In all groups, 12 patients fulfilled the criteria for an insufficient testosterone response from 28 to 364 days. Of these patients, four of 207 (1.9%) and two of 202 (1.0%) were in the degarelix 240/80 and 240/160 mg groups, respectively, and six of 201 (3.0%) were in the leuprolide group.

From day 0–28, treatment with degarelix resulted in a rapid suppression of testosterone levels; by day 3, the median testosterone levels were ≤ 0.5 ng/mL in 96.1%

and 95.5% of patients in the degarelix 240/80 and 240/160 mg groups, respectively (median testosterone levels 0.24 and 0.26 ng/mL, respectively; Fig. 4). By contrast, for patients receiving leuprolide, the median testosterone levels increased by 65% from baseline by day 3 (median testosterone level 6.30 ng/mL; $P < 0.001$). In the leuprolide group, the median testosterone levels were >0.5 ng/mL until the measurements on day 28 (Fig. 4). From this point, testosterone levels were suppressed in all patients in all treatment groups. The median testosterone levels were 0.082, 0.088 and 0.078 ng/mL in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively, from 28 to 364 days.

Of the 201 patients in the leuprolide group, 23 (11%) received concomitant bicalutamide for flare protection at the start of treatment. Of the 178 patients in the leuprolide group who

FIG. 3. The median (quartile) testosterone levels over time (ITT population).

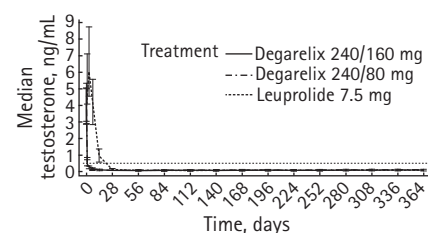
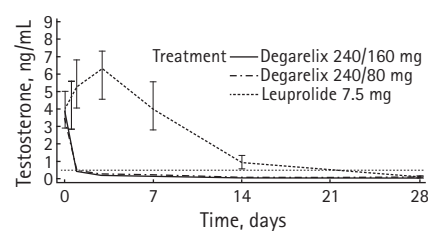


FIG. 4. The median serum testosterone (ng/mL) during the first month of treatment.



did not receive bicalutamide, 144 (81%) had a surge in testosterone (defined as a testosterone increase of $\geq 15\%$ from baseline, on any 2 days during the first 2 weeks). In those one leuprolide who received bicalutamide, 17 (74%) had a testosterone surge. Among the 40 patients in the leuprolide group who did not fulfil the pre-set criteria for a testosterone surge, about half had one testosterone value of $\geq 15\%$ from

FIG. 5. The median serum PSA level (change from baseline) during the first 2 months of treatment in (A) all patients and (B) all those on degarelix, and in those on leuprolide who received bicalutamide for antiflare protection at the start of the treatment (at the discretion of the investigators).

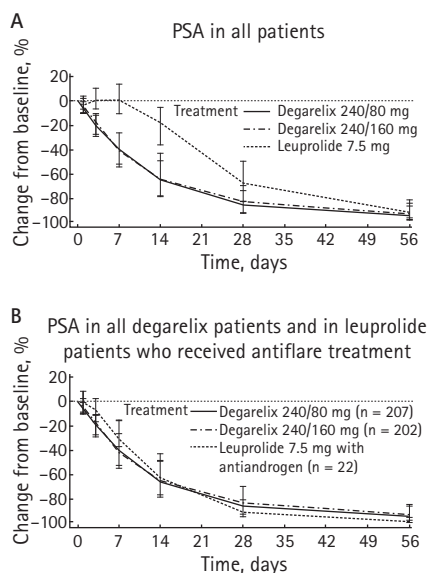
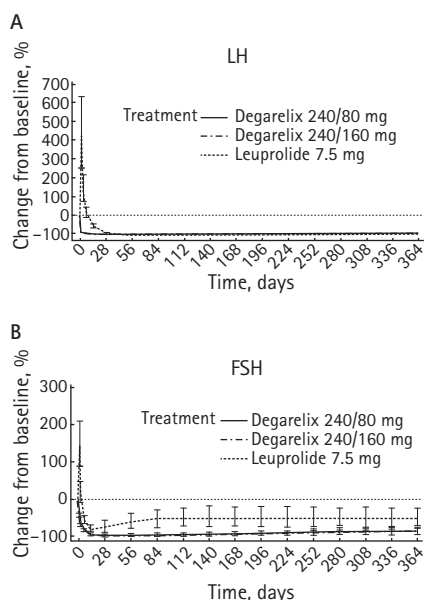


FIG. 6. The median serum (A) LH and (B) FSH levels (change from baseline) during the treatment.



baseline during the first 2 weeks. None of the patients receiving degarelix had a testosterone surge.

In addition to the monthly measurements, testosterone levels were assessed to measure

the agonist stimulation of testosterone ('microsurge') on day 255 and on day 259, 3 and 7 days after the ninth leuprolide injection. The largest value at day 255 or day 259 was used and compared with testosterone levels on day 252. In the two degarelix groups, the mean testosterone levels were slightly decreased on day 255/259 compared with day 252, while in the leuprolide group there was a statistically significant increase of 0.045 ng/mL ($P < 0.001$). In the leuprolide group, eight patients (4%) had testosterone increases of >0.25 ng/mL while four (2%) of these patients reached a testosterone level of >0.5 ng/mL. No testosterone microsuges were detected in patients treated with degarelix.

After 14 days, PSA levels had declined by 64%, 65% and 18% from baseline in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively; after 28 days, the PSA declines were 85%, 83% and 68%, respectively (Fig. 5A). The differences in the reduction in PSA from baseline between degarelix and leuprolide patients at days 14 and 28 were statistically significant ($P < 0.001$).

In the subgroup of patients receiving leuprolide and concomitant bicalutamide, the PSA reduction was more rapid than in those who only received leuprolide, and similar to that of those on degarelix (Fig. 5B). The incidence of PSA failure (defined as PSA increase of $\geq 50\%$ from nadir and ≥ 5 ng/mL on two consecutive occasions at least 2 weeks apart) during the study was similar among the three groups, at 8.9% with degarelix 240/80 mg, 14.2% with degarelix 240/160 mg and 14.1% with leuprolide.

After administration of degarelix, the median LH and FSH levels decreased rapidly and remained suppressed until the end of the study (Fig. 6A,B). By contrast, there was an increase in median LH and FSH levels for patients in the leuprolide group at the beginning of treatment, and FSH levels did not fall to the same extent as they did in both the degarelix arms. At the end of the study, mean FSH levels had decreased by 88.5%, 89.0% and 54.8%, vs baseline, in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively (Fig. 6B).

Treatment-emergent AEs were reported for 79%, 83% and 78% of patients in the degarelix 240/80 mg, degarelix 240/160 mg

and leuprolide groups, respectively (Table 4). Most reported AEs were of mild to moderate intensity (Table 4) [17]. The most frequently reported AE was flushing, by 53 (26%) and 52 (26%) patients in the degarelix 240/80 mg and 240/160 mg groups, respectively, and 43 (21%) patients in the leuprolide group. The s.c. degarelix injection was associated with a higher rate of injection-site reactions than the i.m. leuprolide injection (40% vs $<1\%$, $P < 0.001$, respectively). The local reactions occurred predominantly after the first injection; 33% of 409 starting-dose injections and 4% of 2244 and 2208 maintenance-dose injections (240/80 and 240/160 mg groups, respectively) were reported to be associated with injection-site reactions. Injection-site reactions were documented as mild or moderate in intensity by the patient/investigator; five (1%) of the degarelix patients discontinued due to an injection-site reaction. More patients in the leuprolide group than in the degarelix groups reported arthralgia (9% vs 4%, $P < 0.05$, respectively) and UTI (9% vs 3%, $P < 0.01$, respectively), and more patients in the degarelix groups reported chills (4% vs none, $P < 0.01$, respectively; Table 4). The reported chills generally occurred 5–10 h after administration of degarelix and typically lasted for ≤ 24 h. None of these events were considered to be serious. Although some patients reported one of these events after two or three degarelix injections, in most cases the events did not recur upon re-exposure. Cardiovascular side-effects (e.g. angina pectoris, atrial fibrillation, cardiac failure, and myocardial ischaemia) were reported by 13% of patients in the leuprolide group and by 9% in the degarelix groups ($P = 0.089$).

A similar number of degarelix (7%) and leuprolide (6%) patients had alanine aminotransferase (ALT) levels of more than three times the upper limit of normal (ULN) range, but none of these patients had a concomitant increase in bilirubin of $>1.5 \times$ ULN. The somewhat uneven reports of ALT/aspartate aminotransferase (AST) elevations as AEs (Table 4) do not correspond to uneven deviations of the actual laboratory values, and might represent a reporting bias in this open-label trial. The increases in ALT were reversible; in only a few cases could reversibility not be determined, as there were no further measurements available after the patient completed or discontinued the study. There were increases in body weight of $\geq 7\%$

from baseline in 8% and 13% of patients on degarelix 240/80 and 240/160 mg, respectively, and in 13% of patients on leuprolide.

Serious AEs were reported by 21 (10%) and 24 (12%) patients in the degarelix 240/80 and 240/160 mg groups, respectively, and 28 (14%) in the leuprolide group. AEs resulting in discontinuations were reported by 15 patients (7%) in the degarelix 240/80 mg group, 19 (9%) in the 240/160 mg group, and 12 (6%) in the leuprolide group. The number of discontinuations due to AEs was similar in the three groups. More patients died in the leuprolide group (nine, 4%) than in both degarelix groups (five, 2%, each); none of the deaths were considered to be related to study drugs (Fig. 2).

In all, 10 (5%) and 14 (7%) patients from the 240/80 and 240/160 mg groups, respectively, discontinued due to nonfatal AEs, compared with three (1%) in the leuprolide group. Nonfatal AEs giving rise to discontinuation in the degarelix groups (one, unless otherwise stated) were: injection-site induration, injection-site soreness (four), malignant lymphoma, progression of prostate cancer (five), squamous cell carcinoma, cerebral stroke, cold chills, hot flashes, myocardial infarction, unstable angina, worsening of bone metastases, hypersensitivity (general itching at injection site), alcohol withdrawal symptoms, elevated liver enzymes, osteoarthritis, mild mental status change, and depression. In the leuprolide group, nonfatal AEs giving rise to discontinuation were medication error, progression of prostate cancer, and cerebral aneurysm.

Very few patients in the degarelix groups (<1%) or the leuprolide group (2%) had a markedly abnormal QT interval corrected for heart rate using Fridericia's formula (QTcF) (≥ 500 ms) values after 12 months of treatment, and there were no marked differences in the findings of physical examinations among the groups.

DISCUSSION

This prospective comparative trial was conducted to evaluate the effect of two doses of degarelix (240/80 and 240/160 mg) vs leuprolide (7.5 mg) in patients with prostate cancer. Degarelix is a new drug belonging to the GnRH receptor blocker (antagonist) class

TABLE 4 Incidence and intensity of treatment-emergent AEs ($\geq 5\%$ in any group)

AE, n (%)	Degarelix			Leuprolide 7.5 mg
	240/80 mg	240/160 mg	Pooled	
ITT analysis set	207	202	409	201
Any	163 (79)	167 (83)	330 (81)	156 (78)
Injection-site reactions§	73 (35)	89 (44)	162 (40)	1 (<1)†
Hot flush	53 (26)	52 (26)	105 (26)	43 (21)
ALT increase	20 (10)	17 (8)	37 (9)	11 (5)
Weight increase	18 (9)	22 (11)	40 (10)	24 (12)
Back pain	12 (6)	12 (6)	24 (6)	17 (8)
Hypertension	12 (6)	14 (7)	26 (6)	8 (4)
AST increase	10 (5)	11 (5)	21 (5)	6 (3)
Arthralgia	11 (5)	6 (3)	17 (4)	18 (9)*
UTI	10 (5)	3 (1)	13 (3)	18 (9)†
Fatigue	7 (3)	13 (6)	20 (5)	13 (6)
Hypercholesterolaemia	7 (3)	12 (6)	19 (5)	5 (2)
Chills	7 (3)	11 (5)	18 (4)	0†
Constipation	6 (3)	11 (5)	17 (4)	10 (5)
Intensity				
Any	163 (79)	167 (83)	330 (81)	156 (78)
Mild	138 (67)	145 (72)	283 (69)	138 (69)
Moderate	113 (55)	112 (55)	225 (55)	101 (50)
Severe	32 (15)	36 (18)	68 (17)	26 (13)
Life threatening	1 (<1)	2 (<1)	3 (<1)	5 (2)
Death¶	5 (2)	5 (2)	10 (2)	9 (4)

Statistically significant differences between the pooled degarelix and leuprolide groups, * $P < 0.05$, † $P < 0.01$, and ‡ $P < 0.001$. §Injection-site reactions include injection-site pain, erythema, swelling, induration, and nodule. ¶None of the deaths was considered related to study treatment. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [17].

of agents, whereas leuprolide is an LHRH agonist, the current standard treatment for inducing AD in patients with prostate cancer. The present trial shows that both degarelix dose regimens achieved sustained testosterone suppression with a lower limit of the 95% CI for the cumulative probability of a testosterone level of ≤ 0.5 ng/mL from day 28–364 for degarelix of $\geq 90\%$. Moreover, both degarelix doses were at least as effective as leuprolide at inducing and sustaining testosterone suppression to castrate levels (≤ 0.5 ng/mL) throughout the treatment period.

Analysis of serum testosterone, LH, FSH and PSA highlights the different mechanism of action between degarelix and leuprolide during the first 28 days and throughout the treatment period. In the degarelix groups, the median testosterone level was reduced by $>90\%$ by day 3, compared with a 65% surge in the median testosterone level in the leuprolide group. This contrasting physiological response is a consequence of

the marked suppression of LH from baseline by 88% on day 1 for degarelix, compared with a surge in LH in the leuprolide group ($>400\%$ increase from baseline on day 1). Similarly, there was a more rapid decrease in FSH after degarelix treatment, and the FSH levels did not fall to the same extent with leuprolide. The significance of this latter finding remains undetermined [18,19].

GnRH agonist re-administration has been documented to raise testosterone (acute-on-chronic response or microsurge) [20]. Berges and Bello [21] suggested that an increase in testosterone level to >0.5 ng/mL might be clinically relevant, with potential implications for treatment. Morote *et al.* [22] found a relationship between testosterone suppression and androgen-independent progression. The clinical significance of testosterone microsurgings and breakthroughs [9,23] has not been established. In the present study, we analysed testosterone data on day 252, 255 and 259, to evaluate the incidence of testosterone microsurgings. Eight patients (4%)

in the leuprolide group had microsurgers, with testosterone breakthrough (>0.5 ng/mL) occurring in four of them. There were no microsurgers in any patient on degarelix.

Biochemical evidence of clinical response was indicated in all treatment groups by the steady decrease in PSA levels during the 12-month study; there was a significantly greater decrease in PSA levels at days 14 and 28 in the degarelix groups than in the leuprolide group, reflecting a more rapid response to treatment.

In an attempt to avoid clinical flare in patients receiving leuprolide, an antiandrogen could be added at the start of treatment, at the discretion of the investigator [24]. Degarelix monotherapy provided a similar PSA decrease to the subgroup of patients who received leuprolide with concomitant antiandrogen (11% of the leuprolide patients). Thus, degarelix provided effective AD, with fast onset of action and with sustained testosterone control, without the need for antiandrogen flare protection.

Both degarelix and leuprolide were well tolerated in the study and the number of discontinuations due to AEs was not statistically significant. The higher incidence of injection-site reactions reported with degarelix predominantly occurred after the first injection; ≈1% of the patients in the degarelix groups discontinued due to injection-site reactions. The difference in injection-site reactions might be due to the different forms of administration (s.c. vs i.m.) and the injection volume. Local injection-site reactions were also reported with LHRH agonists when given s.c [25,26]. There was also a higher incidence of chills reported with degarelix. While in some situations, chills can be indicative of an allergic reaction, in the current study no systemic allergic reactions were reported with degarelix. In the present study, there was a significantly lower reported incidence of musculoskeletal events (arthralgia) and UTI with degarelix as compared with leuprolide.

It is important to acknowledge the limitations associated with the present study. The open nature of the study design is an obvious limitation, especially in the interpretation of reported AEs. However, clearly blinding was not possible due to the different routes of administration of the two study drugs, although the laboratory personnel were unaware of the treatment. The leuprolide

monthly dosage of 7.5 mg is standard treatment in USA and, whereas some European countries have a lower registered dose of leuprolide, the dose was considered to be an appropriate high-dose comparator in this study. From a safety perspective, most AEs were related to AD and are therefore not necessarily dose-related. In the present study, administration of an antiandrogen (bicalutamide) in addition to leuprolide 7.5 mg was left to the investigator's discretion. This reflected the fact that co-administration of an antiandrogen is not standard care and depends upon both the individual patient and the stage of the disease.

This randomized study provides comparative data between a LHRH agonist and degarelix for hormonal effects and safety during 1 year of treatment. The mechanistically inherent difference in onset of action has an apparent clinical value for some patient groups (those with advanced disease with symptoms or a risk of symptoms, and those planned for short-term treatment like neoadjuvant, adjuvant or intermittent treatment) where there is no need for antiandrogen flare protection. It remains to be established through further studies whether the faster onset of action, the absence of surges and microsurgers, the more effective FSH suppression, the possibility of a further different safety profile, or any other hitherto unmeasured difference between agonist and blocker provide further clinical value.

In conclusion, degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1-year treatment period. The degarelix regimens of 240/80 and 240/160 mg achieved a more rapid reduction of testosterone and PSA levels than leuprolide. Neither degarelix dosing schedule induced testosterone surge or microsurgers. Degarelix represents a new effective therapy for inducing and maintaining AD for 1 year in patients with prostate cancer. Its immediate onset of action achieves a faster control of testosterone and PSA levels than leuprolide, with no need for flare protection.

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CONFLICT OF INTEREST

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Abbreviations: AD(T), androgen-deprivation (therapy); ALT, alanine aminotransferase; AST, aspartate aminotransferase; AE, adverse event; ITT, intent-to-treat; PP, per protocol; ULN, upper limit of normal.