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# Degarelix versus Goserelin (+ Antiandrogen Flare Protection) in the Relief of Lower Urinary Tract Symptoms Secondary to Prostate Cancer: Results from a Phase IIIb Study (NCT00831233)

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**Key Words**
Degarelix · Goserelin · Lower urinary tract symptoms · Prostate cancer

**Abstract**
***Introduction:*** No studies to date have assessed the efficacy/tolerability of degarelix in the relief of lower urinary tract symptoms (LUTS) secondary to prostate cancer (PrCa). ***Methods:*** Patients were randomised to degarelix 240/80 mg or goserelin 3.6 mg + bicalutamide flare protection (G+B); both treatments were administered for 3 months. The primary endpoint was change in International Prostate Symptom Score (IPSS) at week 12 compared with baseline. ***Results:*** This study was stopped early due to recruitment difficulties. 40 patients received treatment (degarelix n = 27; G+B n = 13); most had locally advanced disease and were highly symptomatic. Degarelix was non-inferior to G+B in reducing IPSS at week 12 in the full analysis set (p = 0.20); the significantly larger IPSS reduction in the per-protocol analysis (p = 0.04) was suggestive of superior reductions with degarelix. Significantly more degarelix patients had improved quality of life (IPSS question) at week 12 (85 vs. 46%; p = 0.01). Mean prostate size reductions at week 12 were 42 versus 25% for patients receiving degarelix versus G+B, respectively (p = 0.04; post hoc analysis). Most adverse events were mild/moderate; more degarelix patients experienced injection site reactions whereas more G+B patients had urinary tract infections/cystitis. ***Conclusion:*** In 40 men with predominantly locally advanced PrCa and highly symptomatic LUTS, degarelix was at least non-inferior to G+B in reducing IPSS at week 12.


## Introduction

Lower urinary tract symptoms (LUTS) are common in elderly men with benign prostatic conditions or prostate cancer (PrCa) and frequently lead to them seeking medi-

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cal care [1]. For this reason, LUTS are often present at the time of diagnosis of PrCa. LUTS are commonly subdivided into three categories: voiding or obstructive (hesitancy, slow stream, intermittency, incomplete emptying); storage or irritative (frequency, urgency, nocturia, urgency urinary incontinence), and post-micturition (postvoid dribbling) [2]. These symptoms can have a considerable impact on patients' quality of life (QoL) and general well-being [3], especially when severe [4].

Treatment of LUTS is related to the origin of the symptoms. In patients with PrCa, surgical intervention (radical surgery or transurethral resection) or radiation therapy can have a positive impact. Radical prostatectomy removes the obstruction and may relieve voiding LUTS in men with localised PrCa [5, 6], while outcomes after transurethral prostatectomy in men with more extensive disease are less encouraging [7]. Radiation therapy decreases gland size and may relieve symptoms but can also exacerbate obstructive and irritative symptoms [8, 9]. α-Blockers, 5α-reductase inhibitors and anticholinergics are used in the management of LUTS in patients with benign prostatic conditions [10] and also less commonly to alleviate symptoms in patients with PrCa undergoing radiotherapy [11].

Gonadotropin-releasing hormone (GnRH) agonists or antagonists are commonly used to provide androgen deprivation in patients with PrCa [12, 13]. However, the mechanism of action of GnRH agonists results in an initial surge in testosterone levels, which can stimulate tumour growth and exacerbate clinical symptoms ('clinical flare') [13]. GnRH agonists (+ antiandrogen flare protection) are also a standard treatment for patients with PrCa suffering LUTS. In contrast to GnRH agonists, GnRH blockers (antagonists) immediately block the GnRH receptor, resulting in a fast suppression of testosterone levels, without a surge [13]. A recent phase III trial (CS21) in patients with PrCa demonstrated that degarelix, a new GnRH blocker, was associated with significantly faster testosterone and prostate-specific antigen (PSA) suppression, and was at least as effective as the GnRH agonist leuprolide at suppressing testosterone to castrate levels over a 12-month study period [14]. Furthermore, unlike leuprolide, degarelix was not associated with testosterone surge or microsurges, thus leading to more stable testosterone suppression as well as a longer time to biochemical progression [15].

Here, we present results of the first study (CS28) to assess the efficacy and tolerability of degarelix compared with a standard treatment (goserelin + antiandrogen flare protection) in the relief of LUTS secondary to PrCa.

## Patients and Methods

*Study Design and Patients*

CS28 was a multicentre, randomised, open-label, parallel-group phase IIIb study that aimed to demonstrate that LUTS relief with degarelix was non-inferior to goserelin + antiandrogen (bicalutamide) flare protection based on the reduction in International Prostate Symptom Score (IPSS) at week 12 versus baseline. Patients were randomised 3:1 to either a degarelix starting dose of 240 mg for 1 month followed by monthly maintenance doses of degarelix 80 mg, or to goserelin 3.6 mg/month + bicalutamide 50 mg/day (G+B). Bicalutamide was initiated 3 days before the first goserelin injection and continued for 14 days afterwards (total treatment duration 17 days). Patients were treated for a total of 3 months. Degarelix was reconstituted in water and the starting dose administered as two 3-ml deep subcutaneous injections into the abdominal region; maintenance doses were administered as single 4-ml subcutaneous injections. Goserelin implants were inserted subcutaneously into the abdominal wall. Bicalutamide was administered once daily orally.

Initially, adult patients with histologically confirmed treatment-naïve PrCa (Gleason graded, T3/4) and LUTS, for whom endocrine therapy was indicated, were to be included. However, as the recruitment rate was low, inclusion criteria were widened to include patients with any stage PrCa and those who had received prior treatment with a 5α-reductase inhibitor or an α-adrenoceptor antagonist. However, therapy must have ceased for ≥6 months for patients treated with a 5α-reductase inhibitor and for ≥8 weeks for α-adrenoceptor antagonist treatment, prior to study entry. Prior transurethral resection of the prostate was not permitted. Patients were also required to have a serum PSA level >10 ng/ml, an IPSS ≥12, peak urinary flow ($Q_{max}$) ≤12 ml/s (voided volume ≥150 ml), a prostate size >30 ml (measured by transrectal ultrasound), and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Independent ethics committees reviewed the study protocol, any amendments, and also advertisements used for recruitment. They also reviewed the patient information sheet and the informed consent form, their updates (if any), and any written materials given to the patients. The trial was performed in accordance with the Declaration of Helsinki, in compliance with the approved protocol and amendments, the International Conference on Harmonisation Guidelines for Good Clinical Practice, the European Union Clinical Trials Directive and with local regulatory requirements. Written informed consent was obtained from each patient before any study-related procedure was performed.

*Endpoints*

Change in IPSS at week 12 compared with baseline was the primary endpoint in this study. Secondary efficacy endpoints also compared data at certain study time points with those at baseline, including: IPSS at weeks 4 and 8; $Q_{max}$ at weeks 4, 8 and 12; prostate size (measured by transrectal ultrasound) at week 12; changes in serum testosterone concentration and PSA levels at weeks 4, 8 and 12. QoL (in relation to urinary symptoms) at week 12 was also compared with the baseline assessment and was evaluated by an additional question on the IPSS questionnaire. The response to this question was analysed separately and was not included in the total IPSS score. The question was, 'If you were to spend the rest of your life with your urinary condition the way it

**Table 1.** Baseline characteristics (full analysis set)

| | Degarelix 240/80 mg (n = 27) | Goserelin 3.6 mg + bicalutamide (n = 13) |
|---|---|---|
| Age, years, median (range) | 68 (53–87) | 72 (57–85) |
| Testosterone level, ng/ml, median (range) | 4.2 (1.1–6.7) | 3.9 (2.7–7.4) |
| PSA level, ng/ml, median (range) | 54.5 (8–1,914) | 41.1 (14.6–348) |
| T staging, n (%) | | |
| T1/2 | 5 (19) | 2 (15) |
| T3/4 | 21 (78) | 11 (85) |
| TX[a] | 1 (4) | 0 (0) |
| M staging, n (%) | | |
| M0 | 4 (15) | 2 (15) |
| M1 | 10 (37) | 4 (31) |
| MX[b] | 9 (33) | 7 (54) |
| Gleason score, n (%) | | |
| 5–6 | 2 (7) | 0 (0) |
| 7–10 | 25 (93) | 13 (100) |
| ECOG performance status, n (%) | | |
| 0: fully active | 22 (81) | 11 (85) |
| 1: restricted, but ambulatory | 4 (15) | 1 (8) |
| 2: ambulatory, unable to carry out work | 1 (4) | 1 (8) |
| IPSS total score, mean (SE) | 20.1 (1.1) | 21.1 (1.6) |
| IPSS quality of life score, mean (SE) | 3.6 (0.3) | 3.2 (0.5) |
| $Q_{max}$, ml/s, mean (SE) | 9.3 (0.8) | 8.3 (0.8) |
| Prostate volume, ml, mean (SE) | 53.5 (5.5) | 50.3 (4.5) |

[a] Primary tumour unassessable. [b]Distant disease unassessable.

is now, how would you feel about that?' The possible answers ranged from 'delighted' (a score of '0') to 'terrible' (a score of '6'). The frequency and severity of adverse events (AEs) occurring during this study were also recorded.

*Statistical Methods*

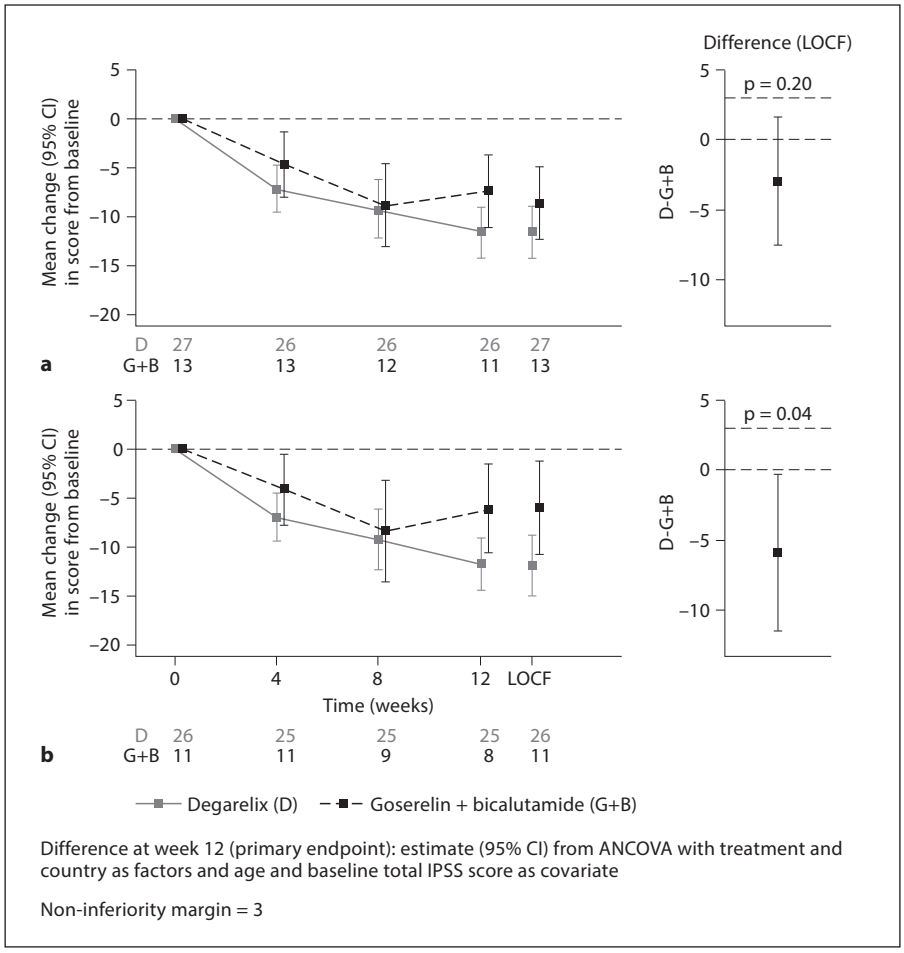
All analyses were performed, and summary statistics calculated, using SAS® version 9.2. Using a non-inferiority margin of 3 points for the true difference in mean change from baseline in total IPSS score between degarelix and G+B, the sample t test ($\alpha = 0.05$, two-sided), and assuming a standard deviation of the change from baseline in total IPSS score of 6.5 points at week 12, 201 degarelix patients and 67 G+B patients were required to demonstrate non-inferiority with 90% probability under the hypothesis of truly equal treatment effects. Since non-inferiority was also planned to be demonstrated in the per-protocol (PP) population, an additional 5% was added to cover for any anticipated protocol violators, to arrive at a planned total population of 280 patients (210 on degarelix; 70 on G+B). The primary analysis was an analysis of covariance (ANCOVA) of the change from baseline in total IPSS score at week 12, using the last observation carried forward (LOCF) approach, with baseline total IPSS and age as covariates, and country/region and treatment as factors in both the full and PP analysis populations. The trial was considered positive if the treatment difference for degarelix versus G+B in the adjusted mean change from baseline in total IPSS was statistically significantly smaller (two-sided at $\alpha = 0.05$ level) than $\Delta = 3$ points in both the full and PP analysis sets.

The full analysis set was defined as all patients who received at least one dose of study drug and had at least one post-dose efficacy assessment. The PP analysis set was defined as patients who were included in the full analysis set who had no major protocol deviations. Observed cases sensitivity analyses (i.e. completer analyses with a week 12 measurement available) were also to be performed.

## Results

*Patients*

The trial was stopped early due to the low recruitment rate and this led to a reduced sample size. In total, 42 patients were randomised; 40 patients received at least one dose of study treatment and had at least one post-dose efficacy assessment and so were included in the full analysis set. Baseline characteristics were generally well balanced between groups (table 1); most had locally advanced or metastatic PrCa, high PSA levels and were highly symptomatic.




Difference at week 12 (primary endpoint): estimate (95% CI) from ANCOVA with treatment and country as factors and age and baseline total IPSS score as covariate

Non-inferiority margin = 3

**Fig. 1.** Mean (95% CI) change from baseline in total IPSS over time: full analysis set (LOCF analysis) (**a**) and PP analysis set (LOCF analysis) (**b**).

*International Prostate Symptom Score*

*Total Score.* Degarelix was non-inferior to G+B in reducing IPSS at week 12 (fig. 1; table 2); mean total IPSS showed clinically significant (>3 points) [16] decreases from baseline in both groups. The upper limit of the two-sided 95% confidence interval (CI) for the adjusted mean difference between the two treatment groups for total IPSS at week 12 was 1.6 and –0.3, for the full and PP analysis sets, respectively. These were below the non-inferiority margin of 3, and so non-inferiority could still be concluded despite the small number of patients in each group. Moreover, for the PP analysis set, the upper limit of the two-sided 95% CI for the difference between the two treatment groups for total IPSS at week 12 (–0.3) was below zero, suggesting statistical superiority of degarelix over G+B (p = 0.04) in IPSS reduction (fig. 1; table 2). Overall, numerically greater reductions in mean total IPSS score were observed at weeks 4, 8 and 12 with degarelix compared with G+B.

*Individual Items.* Compared with those receiving G+B, numerically greater proportions of degarelix-treated patients experienced improvements in the following individual items on the IPSS questionnaire at week 12: incomplete emptying, frequency, intermittency, and nocturia (fig. 2). Numerically greater improvements in weak stream and straining symptoms were seen in the G+B group. Mean QoL scores showed a decrease (i.e. QoL improved) from baseline at each visit in both treatment groups but significantly more degarelix patients had improved QoL at week 12 compared with those receiving G+B (85% (23/27) versus 46% (6/13); p = 0.01) (fig. 2). The mean (standard error (SE)) decrease from baseline in scores at weeks 4, 8 and 12 was also numerically higher in the degarelix group (–1.0 (0.2), –1.5 (0.3) and –1.8 (0.3), respectively) than in the G+B group (–0.5 (0.4), –0.7 (0.7) and –0.6 (0.5), respectively). At week 12, numerically more patients in the G+B group experienced worsening of emptying, intermittency, urgency, weak stream and

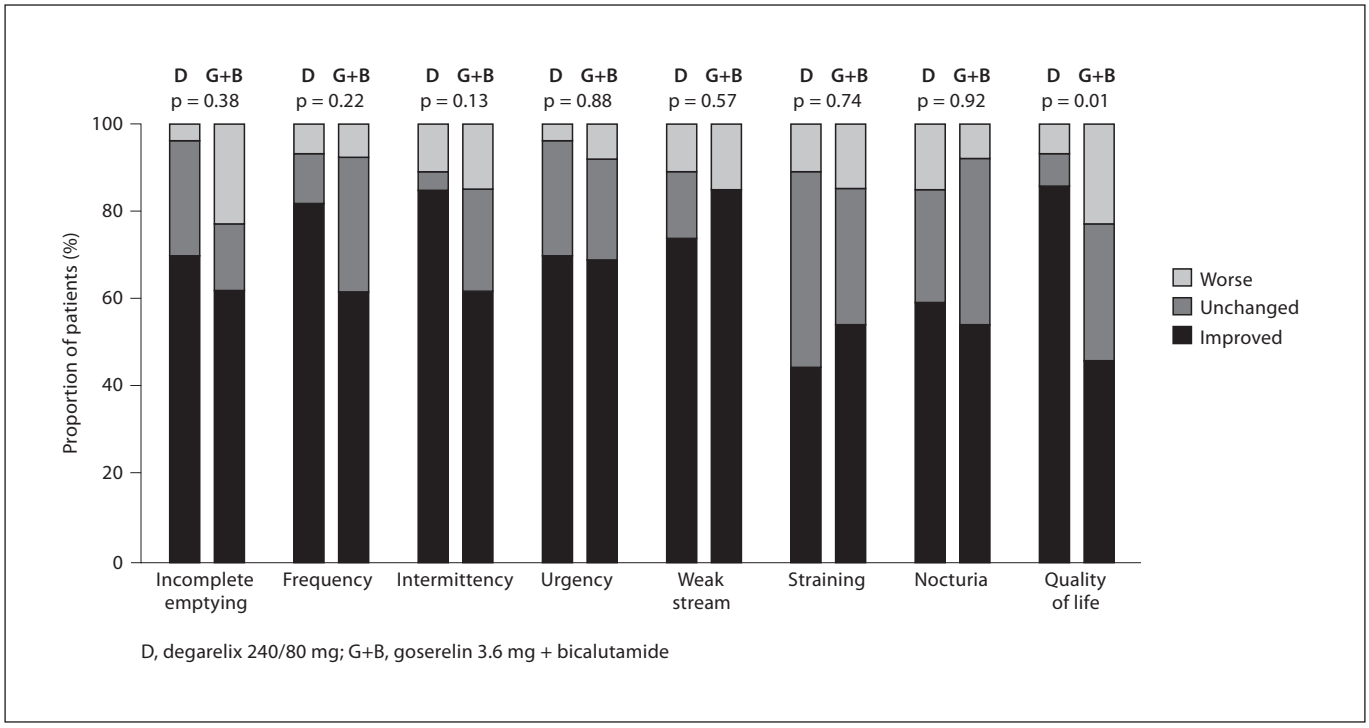



**Fig. 2.** Change from baseline (improved/unchanged/worse) in individual IPSS items at week 12 (full analysis set; LOCF analysis).

straining symptoms, and QoL (fig. 2). In contrast, numerically more degarelix patients had worsened nocturia.

*Prostate Size and $Q_{max}$*

Decreases in prostate size were observed in both groups at week 12, but the magnitude of decrease was numerically greater with degarelix than with G+B. In the full analysis set, adjusted mean (SE) change from baseline was –21.8 (2.7) versus –14.0 (3.9) ml in the two groups, respectively; treatment difference (in favour of degarelix): –7.8; 95% CI –17.3, 1.6; p = 0.10. This equates to 42% (4.5) versus 25% (6.5) mean (SE) percentage reductions in prostate volume at week 12 versus baseline for patients receiving degarelix versus G+B, respectively; treatment difference (in favour of degarelix): –17%; 95% CI –33.0, –1.3; p = 0.04 (post hoc analysis). In the PP analysis, mean (SE) percentage reductions in prostate size at week 12 were –42% (4.7) versus –29% (8.0); p = 0.16, in the degarelix and G+B groups, respectively.

Increases in $Q_{max}$ were observed in both groups at weeks 4, 8 and 12. In the full analysis set at week 12, the mean (SE) change from baseline was 3.3 (1.2) versus 1.3 (1.6) ml/s in the degarelix versus G+B groups, respec-

**Table 2.** Reduction in total IPSS at week 12 compared with baseline

| | Degarelix 240/80 mg (n = 27) | Goserelin 3.6 mg + bicalutamide (n = 13) | Treatment difference[a] (95% CI) | p value[b] |
|---|---|---|---|---|
| *LOCF analyses* | | | | |
| Full analysis set | | | | |
| Number | 27 | 13 | | |
| Mean (SE) | –11.6 (1.3) | –8.6 (1.9) | –3.0 (–7.5, 1.6) | 0.20 |
| PP analysis set | | | | |
| Number | 26 | 11 | | |
| Mean (SE) | –11.8 (1.5) | –5.9 (2.3) | –5.9 (–11.5, –0.3) | 0.04 |
| *Observed cases analyses* | | | | |
| Full analysis set | | | | |
| Number | 26 | 11 | | |
| Mean (SE) | –11.6 (1.3) | –7.4 (1.8) | –4.2 (–8.7, 0.3) | 0.06 |
| PP analysis set | | | | |
| Number | 25 | 8 | | |
| Mean (SE) | –11.7 (1.3) | –6.0 (2.2) | –5.7 (–11.0, –0.4) | 0.04 |

[a] Estimates from an ANCOVA with treatment and country as factors and age and baseline IPSS value as covariates. [b] p value for testing superiority.

tively; treatment difference (in favour of degarelix) was 2.0 ml/s (95% CI –2.0, 6.1; p = 0.32). Similar changes in $Q_{max}$ were observed in the PP analyses.

*Testosterone and PSA Control*

All patients in the degarelix group maintained serum testosterone at or below castrate levels (0.5 ng/ml) at weeks 4, 8 and 12. Results were similar in the G+B group, although 1/13 patients (8%) had testosterone >0.5 ng/ml at week 4. Mean testosterone levels were reduced by >97% in the degarelix treatment group at these time points; mean testosterone levels were reduced by 84% at week 4 in the G+B group and by >97% at weeks 8 and 12.

PSA levels were reduced by >90% at week 12 in both the degarelix and G+B groups (mean reduction 92 versus 97%, respectively). Median PSA levels at this time point were <2 ng/ml in both groups.

*Tolerability*

Overall, 52% (14/27) versus 54% (7/13) of patients in the degarelix versus G+B groups experienced an AE during the study, most of which were mild (common toxicity criteria (CTC) grade 1) or moderate (CTC grade 2) in intensity. Injection site events (33% (9/27 patients)) and hot flushes (19% (5/27 patients)) were the most common AEs in the degarelix group; hot flushes, cystitis, urinary tract infections (UTI) and metastases to bone (15% each (2/13 patients)) were most common in the G+B group.

There were no deaths, discontinuations due to AEs, serious AEs or severe (CTC grade 3–5) AEs in the degarelix group. In those receiving G+B, 1/13 patients (8%) died from renal failure and also had several other serious AEs (hepatic failure, PrCa progression and lower urinary tract obstruction). Severe urinary retention occurred in another patient receiving G+B.

## Discussion

The efficacy and safety of degarelix as a PrCa treatment has been well established in an extensive clinical trial programme [14, 17, 18], but its effect on LUTS has not been studied previously. The current study, therefore, aimed to determine the efficacy and safety of degarelix versus G+B in men with LUTS secondary to PrCa. The target patient population was difficult to recruit fully at the participating sites. Unfortunately, despite several initiatives to improve recruitment (e.g. protocol amendments to broaden the inclusion criteria), this trial was stopped early with 42 patients randomised. Most of these patients had highly symptomatic disease, which reflects the original stringent recruitment criteria. However, because the effect of degarelix on IPSS reduction was greater than expected, it was still possible to show that this agent was non-inferior to G+B at reducing IPSS at week 12 in the full analysis set, despite the reduced sample size. The fact that the observed SD (6.7) was very close to the SD assumed in the original power calculation (6.5), also provides reassurance that the original power calculations were appropriate. Furthermore, sensitivity analyses in the PP population suggested that these results were robust and the significantly larger reductions in IPSS in these analyses are suggestive of degarelix being superior to G+B for this endpoint. This result is consistent with the statistically significant benefits observed for degarelix in percentage change in prostate size and QoL (IPSS question). There were also numeric improvements seen in both selected voiding (incomplete emptying and intermittency) and storage (frequency and nocturia) symptoms, as well as $Q_{max,}$ although these did not reach statistical significance. Due to the low number of patients included, any imbalances between groups could have biased the results. However, it is important to note that these data were corrected via ANCOVA for various baseline factors (country, age and baseline value). Nonetheless, it must be acknowledged that the smaller the sample size, the greater the likelihood that any observed differences between treatments could be due to chance, and so these results should be interpreted within the context of the size of the study.

The numerically higher frequency of cystitis/UTI in patients receiving G+B seems to be in agreement with the less pronounced effect on prostate size and lower urinary tract obstruction. The mean percentage reduction in prostate volume observed for G+B at week 12 in the present study (25%) is similar to the mean 3-month reduction of 31% seen in patients receiving buserelin + nilutamide in a recent neoadjuvant study [19]. Other combination neoadjuvant treatments such as bicalutamide + dutasteride have produced similar prostate size reductions to the GnRH agonists (34% reduction after 3 months) [20]. In the present study, degarelix achieved a mean reduction of 42% at week 12; a similar reduction was only seen after 6 months' buserelin + nilutamide treatment. Interestingly, benefits in prostate size reduction have also been noted for degarelix versus GnRH agonists in animal models of PrCa [21].

Testosterone control appeared to be similar between groups in this study; however, as the first post-baseline measurement was at week 4, early differences would have been missed. Any initial testosterone flare produced by

GnRH agonists may translate into a delay in the onset of tumour inhibition (and, therefore, potentially a delay in symptom control) compared with degarelix, which offers immediate testosterone suppression. The apparent efficacy benefits of degarelix may relate to the differences in mode of action between these two agents; however, the differences in prostate size and $Q_{max}$ may not be solely attributable to differences in the onset of testosterone suppression. This raises the possibility of other driving mechanisms that were not directly addressed by the present study. For example, experimental observations suggest that GnRH antagonists may have direct effects on prostate cells including pro-apoptotic [22] and antiproliferative effects [23], regulation of growth hormones [24], and even anti-inflammatory effects [25]. However, such preclinical observations are yet to be verified in patients with PrCa. GnRH antagonists are also associated with a more profound and sustained suppression of follicle-stimulating hormone levels compared with GnRH agonists [14]. This observation is of interest as evidence is accumulating that follicle-stimulating hormone may have a direct role in the pathogenesis and progression of PrCa [26–30]. Together, such effects could in theory contribute to a more rapid and/or more pronounced shrinkage of prostate tumours during treatment with degarelix as compared with G+B.

Overall, the tolerability profiles of these treatments were as expected for a population of men with LUTS secondary to PrCa. These data were also in line with previous findings for degarelix versus a GnRH agonist [14]; injection site events were more common with degarelix and UTIs/cystitis/obstruction were more common with G+B. Both treatments were generally well tolerated, with most AEs being mild or moderate in intensity. However, 1 patient experienced serious AEs (one of which was fatal) and another had a severe AE related to urinary retention (both patients received G+B). These AEs are in line with the less pronounced prostate shrinkage and $Q_{max}$ improvements seen in this group, which in turn may be a consequence of its different mode of action. Ultimately, the overall efficacy and tolerability findings translated into improved QoL, irrespective of treatment received. However, significantly more degarelix patients experienced a QoL improvement at week 12 compared with those receiving G+B.

## Conclusions

Degarelix was non-inferior to G+B at reducing LUTS at week 12 in these 40 patients with mostly highly symptomatic, advanced disease; the PP analyses were suggestive of degarelix being superior to G+B for this endpoint. Significantly greater improvements in percentage change in prostate size from baseline and QoL were also seen in the degarelix group. These results are supported by a larger numeric improvement in $Q_{max}$ and a lower incidence of urinary AEs during degarelix treatment. Collectively, these observations suggest that the greater LUTS improvement could be attributed to a more pronounced shrinkage of the prostate and consequently improved urinary flow and bladder emptying in the patients treated with degarelix. Nonetheless, these results should be interpreted within the context of the size of the study.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## Disclosure Statement

John Anderson has previously received honoraria from Ferring Pharmaceuticals and Manfred Wirth has worked as a consultant and lecturer for this company. Enrico Colli, Egbert van der Meulen and Bo-Eric Persson are employees of Ferring Pharmaceuticals. Ghandi Al-Ali, Joan Benejam Gual and Francisco Gomez Veiga have no conflicts of interest to declare.

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