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Degarelix Versus Goserelin Plus Bicalutamide In The Short-Term Relief Of Lower Urinary Tract Symptoms In Prostate Cancer Patients: Results Of A Pooled Analysis

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Background: In patients with prostate cancer (PCa), prostate enlargement may give rise to lower urinary tract symptoms (LUTS); many patients suffer from moderate-to-severe symptoms. We compare the efficacy of degarelix and goserelin plus bicalutamide in improving LUTS in PCa patients.

Methods: Data were pooled from three Phase 3, randomised clinical trials of once-monthly treatment for 12 weeks with degarelix (240/80 mg; n = 289) or goserelin (3.6 mg) plus bicalutamide (50 mg; n = 174) for initial flare protection. LUTS at weeks 4, 8, and 12 were compared to baseline. Clinically relevant LUTS relief was a ≥3-point international prostate symptom score (IPSS) decrease. Adverse events were assessed throughout the trials.

Results: Patients receiving degarelix had significantly greater decreases in IPSS vs. goserelin at week 12 (adjusted difference: -1.24; 95% CI -2.33 to -0.14, *P* = 0.03). Clinically relevant LUTS relief with degarelix was especially pronounced in patients with moderate-to-severe LUTS (baseline IPSS ≥13) (odds ratio; OR 2.31; 95% CI 1.19 to 4.47, *P* = 0.01) and advanced PCa (OR 2.36; 95% CI 1.10 to 5.04, *P* = 0.03). A two-fold higher OR for early (week 4) LUTS relief was seen with degarelix vs. goserelin (OR 2.03; 95% CI 1.14 to 3.60, *P* = 0.02). No difference in total prostate volume or urinary tract infection-related adverse events (2%) was seen between treatment groups.

Conclusion: An early, significant and clinically more pronounced improvement of LUTS, especially in patients with moderate-to-severe LUTS or advanced PCa, was seen with degarelix vs. goserelin plus bicalutamide.

Keywords LUTS, degarelix, goserelin, bicalutamide

1. INTRODUCTION

Lower urinary tract symptoms (LUTS) increase in prevalence and severity with age, representing a major burden for the ageing male population, adversely affecting all aspects of quality of life and general well-being [1-3]. Symptomatic LUTS are common in elderly men with benign prostatic conditions and are associated with an increased likelihood of a subsequent prostate cancer (PCa) diagnosis [4]. In patients with PCa, the growth of the prostate due to benign prostatic hyperplasia as well as the tumour may give rise to LUTS, and almost 45% of PCa patients suffer from moderate-to-severe symptoms [5, 6]. The international prostate symptom score (IPSS) is a 7-item questionnaire giving a total score of between 0 (no LUTS) and 35 (severe LUTS) and is a widely used instrument to assess the severity of LUTS during the preceding 4 weeks [7].

Treatment of LUTS is related to the underlying diagnosis and alpha-blockers, 5-alpha-reductase or anticholinergic agents are currently used as therapeutic options to alleviate symptoms in patients with benign prostatic disorders [8]. In patients with PCa, radiation therapy may positively impact LUTS by decreasing gland size but can also exacerbate urinary tract symptoms [9]. Hence, the negative impact of LUTS combined with the lack of appropriate treatment methods imply an increased medical need for reducing LUTS in patients with PCa.

Androgen-deprivation therapy (ADT) is commonly used in the management of locally advanced PCa to reduce prostate volume [10-12] and potentially down-stage the disease before radiotherapy [13]. Neo-adjuvant hormonal therapy prior to radiation therapy is also becoming more commonly used as it has been shown to improve overall survival [13]. Luteinising hormone-releasing hormone (LHRH) receptor agonists cause an initial surge of testosterone, which might stimulate tumour growth and exacerbate clinical symptoms [14]. LHRH agonists therefore have to be co-administered with antiandrogens to avoid such complications [15]. By contrast, gonadotropin-releasing hormone (GnRH) antagonists

promptly block the GnRH receptor, thereby quickly suppressing luteinising hormone, follicle-stimulating hormone and consequently testosterone production without surge [13, 16].

There is limited information on the impact of short-term ADT on LUTS relief in PCa patients using different ADTs; however three Phase 3b studies have compared the effect of the antagonist (degarelix) and agonist (goserelin) on LUTS relief, prostate volume reduction and testosterone suppression after 12 weeks of treatment in patients with all stages of PCa [17-19]. Total prostate volume (TPV) and testosterone suppression to castrate levels were similar for both ADTs, however, significantly greater LUTS relief was observed in patients with moderate-to-severe symptoms at baseline treated with degarelix compared with goserelin and bicalutamide [17, 18].

We present a pooled analysis, based on individual patient level data, of the three randomised controlled Phase 3b trials, comparing the effect of degarelix with goserelin in reducing LUTS and other prostate-related variables in patients with different stages of PCa.

2. PATIENTS AND METHODS

2.1 Study design

Data from three previously published randomised, parallel-arm, active-controlled, open-label, multicentre, 12-week Phase 3b clinical studies were pooled. The designs of the three studies (CS28, CS30 and CS31) were similar with regard to prospective controlled assessments, and have been presented in detail elsewhere [17-19]. However, there were minor differences in the enrolled patient population: Study CS28 included mostly metastatic cancer patients due to an inclusion criterion of an IPSS score ≥12 at baseline and only four patients with localised PCa were registered. The study was terminated early due to recruitment difficulties, and consequently fewer patients than planned were enrolled. In study CS30, where neoadjuvant ADT prior to radical radiotherapy was pre-planned, no patients had metastatic PCa (Table 1). All three studies were reviewed by independent ethics

committees, performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice and with local regulatory requirements. Patients provided written informed consent.

2.2 Patients

In all three studies, adult patients aged 18 years or older with histologically confirmed PCa, suitable for ADT with serum prostate-specific antigen (PSA) levels >2 ng/ml and TPV >30 ml were included. Baseline parameters included demographic data, medical history, vital signs, medications, and PCa stage. Eligible patients were randomised 3:1 to receive treatment once-monthly at weeks 4, 8, and 12 with either degarelix injections (starting dose of 240 mg and subsequent maintenance doses of 80 mg) or goserelin implants (3.6 mg) plus 50 mg once-daily oral treatment with bicalutamide as anti-androgen flare protection for the first 17–28 days. An exclusion criteria in all three trials was treatment with a 5-α reductase inhibitor in the previous 6 months or treatment with an alpha-adrenoceptor blocker in the previous 4 weeks.

In order to analyse any potential treatment benefits associated with a particular subgroup of patients, a number of clinically relevant subgroups were defined: moderate-to-severe LUTS (total IPSS score ≥13 at baseline), dominance of voiding symptoms at baseline, TPV >40 ml at baseline, disease stage according to TNM staging (localised: T1–2 and NX; or N0 and M0; locally advanced: T 3–4 and [NX or N0] and M0; metastatic: [N1 and M0]; or M1). For the current analysis locally advanced and metastatic are also combined as ‘advanced’ PCa.

2.3 Assessments

The severity and change in LUTS were evaluated based on the IPSS questionnaire [7], containing seven questions regarding incomplete emptying, frequency, intermittent stream, urgency, poor stream, straining, and nocturia. Each question was assigned a score of 0 to 5. A score of ‘0’ corresponds to a response of ‘not at all’ for the first six symptoms and

‘none’ for nocturia, and a score of 5 corresponds to a response of ‘almost always’ for the first six symptoms and ‘5 times or more’ in case of nocturia. Dominance of voiding symptoms was defined in patients when the weighted voiding score (sum of voiding symptom scores divided by the maximum possible voiding score of 20) is greater than the similarly weighted storage score (maximum possible score of 15).

The IPSS was recorded before dosing at baseline and at weeks 4, 8, and 12. A clinically meaningful response (responder) was defined as an IPSS reduction of at least 3 points from baseline [20]. Further prostate-related assessments in all trials included serum testosterone, PSA and prostate volume as assessed by the investigator using trans-rectal ultrasound. Blood samples for analyses of testosterone and PSA were collected at each monthly visit before administration of the drug. Adverse events were assessed throughout the trials and classified according to the Medical Dictionary for Regulatory Activities version 15.0.

2.4 Statistical methods

The change from baseline in total IPSS was analysed using a repeated measures analysis of covariance (ANCOVA) model, and the associated responder status was analysed using a repeated logistic regression model with generalised estimation equations. Both models included the following factors: treatment, month, study and PCa stage (non-classifiable, localised, locally advanced and metastatic); and covariates: baseline IPSS, age, body mass index (BMI), log PSA, testosterone and TPV. To allow for changes of treatment differences in time, a treatment by visit (week 4, 8 or 12) interaction term was included in both models. To test for heterogeneity of effects across studies, a study by treatment interaction term was included in the models and tested for significance. In case of non-significance, this interaction term was excluded.

For repeated ANCOVA and repeated logistic regression model, adjusted treatment difference in mean effects estimates and adjusted odds ratios (ORs) estimates are provided, respectively. Adjusted treatment differences at visits and average values over the

observational period are accompanied by 95% confidence intervals (CI) and p-values (based on the t-test and the Wald test, for the ANCOVA, and logistic models, respectively).

These analyses are conducted in the full analysis set comprising all randomised and dosed subjects, who had at least one post-baseline efficacy assessment. In contrast to the analyses performed in the individual trials [17-19], IPSS questionnaires with any incomplete items were not included in these analyses (*n* = 21). Identical analyses were performed in the patient subgroups detailed above.

The analyses were generated using SAS software, version 9.2. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

3. RESULTS

3.1 Baseline characteristics

The full-analysis set consisted of 463 patients with histologically-confirmed and treatment-naïve PCa; 289 patients received degarelix and 174 patients received goserelin plus bicalutamide. Patient demographics and baseline characteristics were generally similar between the treatment groups (Table 2). No significant differences were seen in age, BMI, TPV, testosterone, PSA or total mean IPSS between the treatment groups at baseline. Almost half of the patients in both groups reported moderate-to-severe LUTS at baseline and approximately two-thirds of patients in both groups had enlargement of the prostate (TPV >40 ml) at baseline when assessed by trans-rectal ultrasound. Over half of the patients in both treatment groups had dominance of storage symptoms. A slightly higher proportion of patients in the degarelix group compared with goserelin patients, had localised PCa (48% vs. 42%, respectively) and locally advanced PCa (34% vs. 25%, respectively) at baseline. Consequently, the proportion of metastatic cancer patients at baseline was slightly lower in the degarelix than in the goserelin treated group (11% vs. 20%, respectively).

3.2 Study heterogeneity

As a sensitivity analysis for possible study heterogeneity, a study-by-treatment interaction term was included in the models. The p-values in the linear and logistic models did not demonstrate significance, indicating homogenous study outcomes. The interaction term was therefore not included in the final regression models.

3.3 Adjusted mean changes from baseline

The mean change in IPSS showed a progressive decrease from baseline for both treatment groups in the overall patient population (Figure 1A) reaching clinical significance (>3 point reduction in IPSS) at week 8. For patients with baseline moderate-to-severe LUTS and patients with advanced (locally advanced or metastatic) disease, this occurred at week 4 in both treatment groups (Figures 1 B and D).

Adjusted mean treatment differences are presented in Table 3. The data show a greater mean IPSS reduction at week 12 in patients with degarelix in the overall population (-1.24; 95% CI -2.33 to -0.14, *P* = 0.027). For patients with moderate-to-severe LUTS at baseline the treatment difference for degarelix vs. goserelin at week 12 was (-2.56; 95% CI -4.34 to -0.79, *P* = 0.005). This reflects an adjusted mean IPSS decrease of -8.0 for degarelix vs. -5.4 for goserelin in those with moderate-to-severe LUTS at baseline. The adjusted mean IPSS change was also significantly greater at week 12 in the degarelix group among patients with dominance of voiding symptoms at baseline (Figure 1C) and those with advanced (locally advanced or metastatic) PCa at baseline (-2.30; 95% CI -4.51 to -0.09, *P* = 0.042 and -2.17; 95% CI -3.83 to -0.51, *P* = 0.011, respectively). At week 12, the decrease in IPSS among men with dominance of storage symptoms was -2.48 and -1.6 for degarelix and goserelin plus bicalutamide, respectively, data not shown. This reduction was below the predefined level of a clinically meaningful response (an IPSS reduction of at least 3 points from baseline). The interaction between week and treatment did not indicate any significant trends

in increasing or decreasing differences between the two treatments, except for the moderate-to-severe subgroup (f-test *P* = 0.050).

3.4 Responder analyses

The crude proportion of patients with clinically meaningful LUTS relief (responders) at week 12 was higher in the degarelix group (47%), compared with the goserelin group (39%). When adjusted for potential confounders, the odds of an IPSS decrease of at least 3 points at week 12 were similar for degarelix and goserelin patients in the overall population (OR: 1.52; 95% CI 0.92 to 2.51, *P* = 0.104) (Table 4). However, for patients with moderate-to-severe LUTS at baseline and in those with locally advanced or metastatic cancer stage, degarelix treatment was associated with an increased probability of achieving clinically meaningful LUTS relief (OR: 2.31; 95% CI 1.19 to 4.47, *P* = 0.013 and OR: 2.36; 95% CI 1.10 to 5.04, *P* = 0.027, respectively).

Notably, a higher proportion of degarelix-treated patients had a clinically relevant response to treatment at week 4. Table 4 shows the ORs across treatment visits and patient subgroups. Significant ORs in favour of degarelix were seen at all visits in the group of patients with moderate-to-severe LUTS at baseline and the average change from baseline was significant in all patient groups except those with localised disease. There were no significant changes in ORs during the treatment period in any of the groups.

3.5 Change in serum testosterone, PSA and prostate volume

Median levels of serum testosterone were similar between degarelix and goserelin-treated patients and declined to castration levels from baseline to week 12 in both treatment groups. Median serum testosterone values at study visits at week 4, 8, and 12 were 0.05 ng/ml at all visits for degarelix- and 0.12, 0.05 and 0.05 ng/ml, respectively for goserelin-treated patients.

The PSA level and TPV decreased significantly from baseline to week 12 in both treatment groups, with median percentage decreases in TPV of 37.0% for degarelix and 38.4% for goserelin. Median percentage declines in PSA were 90.6% for degarelix and 95.8% for goserelin.

3.6 Safety

A similar incidence of renal- and urinary tract-related adverse events were seen in the two treatment groups. Treatment-emergent renal or urinary tract adverse events were reported in 13% of degarelix- and 10% of goserelin-treated patients (Table 5), with an equivalent occurrence of urinary tract infections (2%).

4. DISCUSSION

In this pooled, individual patient data-based analysis of three prospective randomised, controlled Phase 3b studies, we evaluated the effect of the GnRH antagonist degarelix and the LHRH agonist goserelin in reducing LUTS during a 12-week observational period in patients suitable for ADT with various stages of PCa. Our data confirm the results of the three individual studies [17-19] reinforcing the treatment benefit of degarelix vs. goserelin in LUTS relief. Despite an equal response in PCa-related efficacy parameters (testosterone suppression, prostate volume and PSA reduction), treatment with degarelix consistently led to a greater reduction in IPSS scores across subgroups of patients, such as subjects with moderate-to-severe LUTS, dominance of voiding symptoms and in patients with advanced PCa. The average responder rate (during the entire treatment period) was significantly higher for degarelix patients in both the overall population and in all subgroups of patients. The higher ORs at week 4 in favour of degarelix also reflect a more rapid and early treatment effect in degarelix patients as opposed to the goserelin group. The results not only illustrate an early noticeable local treatment effect of degarelix compared with goserelin in terms of reducing LUTS by week 4, but also demonstrate that this effect is maintained throughout the 12-week treatment period.

A recent meta-analysis also assessed the effect of degarelix and LHRH agonist therapy on LUTS relief [21]. A systematic review of the literature identified the same three trials as analysed here; the differences between the analyses are that we included adjustments for potential disease-related confounding factors, analysed patient subgroups to determine those men who may benefit most, used ORs to assess clinical significance and performed longitudinal analyses to determine timing of onset of LUTS relief. Cui et al. report a significantly greater reduction in IPSS with degarelix (standardised mean difference -1.85, 95% CI -2.97 to -0.72, *P* = 0.001) and in those with IPSS ≥13 at baseline (standardised mean difference -2.68, 95% CI -4.57 to -0.78, *P* = 0.006) [21]. Our data confirm these findings and provide additional insight into patient subgroups and effects over time, through analyses not possible with a meta-analysis.

The differences in LUTS relief between degarelix and goserelin cannot be attributed to reductions in TPV and testosterone alone as these were achieved to a similar degree in both treatment regimes. A possible mechanism that may contribute to the greater impact of degarelix on urinary symptom relief is the different mechanism of action between LHRH agonists and GnRH antagonists. As extrapituitary GnRH receptors have been identified on epithelial and smooth muscle cells of the prostate, on peripheral lymphocytes infiltrating the prostate and on bladder mucosa [22, 23], degarelix may have a different local effect than agonists on prostate or bladder cells. Experimental observations from *in vitro* and *in vivo* animal studies, suggest that antagonists may have direct effects on prostate cells, including pro-apoptotic [24] and antiproliferative effects [25]. GnRH antagonists are also associated with a more profound and sustained suppression of follicle-stimulating hormone levels compared with agonists [26]. This observation is of interest as evidence is accumulating that follicle-stimulating hormone may have a direct role in the pathogenesis and progression of PCa [27].

Together, such extrapituitary effects on prostate and bladder cells could, in theory, contribute to a more rapid and greater relief in LUTS beyond shrinkage of prostate tumours

during treatment with degarelix compared with goserelin. Although most PCa patients remain asymptomatic for long time, almost 45% of PCa patients suffer from moderate-to-severe LUTS and the majority of prostate tumours are discovered when patients seek medical help for LUTS. Although it remains to be elucidated whether LUTS relief is directly associated with shrinkage of the prostate tumours, one can speculate that a decrease in LUTS may improve local control of PCa, either through bladder protective effects or through pro-apoptotic and antiproliferative effects on prostate cells.

Considering the major burden of LUTS in the ageing male population, the symptom improvement in patients with moderate-to-severe LUTS secondary to PCa can be seen as a clinically meaningful effect in terms of enhanced urinary and bladder functions and improved quality of life and warrants further exploration in future urodynamic studies.

Both medications were safe and well tolerated with no major differences in incidences of adverse events related to the renal and urinary tract. The adverse events reported were in line with previous data in elderly men receiving short-term ADT.

Limitations of our analysis include a trial period which ceased at 12 weeks, so it is not possible to determine whether any beneficial effect on LUTS relief is sustained long-term. Differences in the inclusion criteria between the studies, resulting in slightly different patient populations, might limit the applicability of the findings, therefore the results should be interpreted with caution. Also, additional functional assessment tools relating to LUTS evaluation (e.g. uroflowmetry with post-voiding residual volume) would have strengthened the results. Finally, the assessment of trans-rectal ultrasound were not evaluated centrally, which may result in variability in the TPV results.

In conclusion, the results of this pooled analysis – in agreement with the individual trials and a recent meta-analysis – demonstrate that ADT treatment with the GnRH antagonist degarelix leads to more prominent LUTS relief compared with the LHRH agonist goserelin in PCa patients who are indicated for hormonal therapy. The benefit of degarelix is most

pronounced in patients with moderate-to-severe LUTS or advanced cancer stage at baseline. Therefore, degarelix can be considered an evidence-based and effective alternative to agonists in patients with PCa complicated by LUTS.

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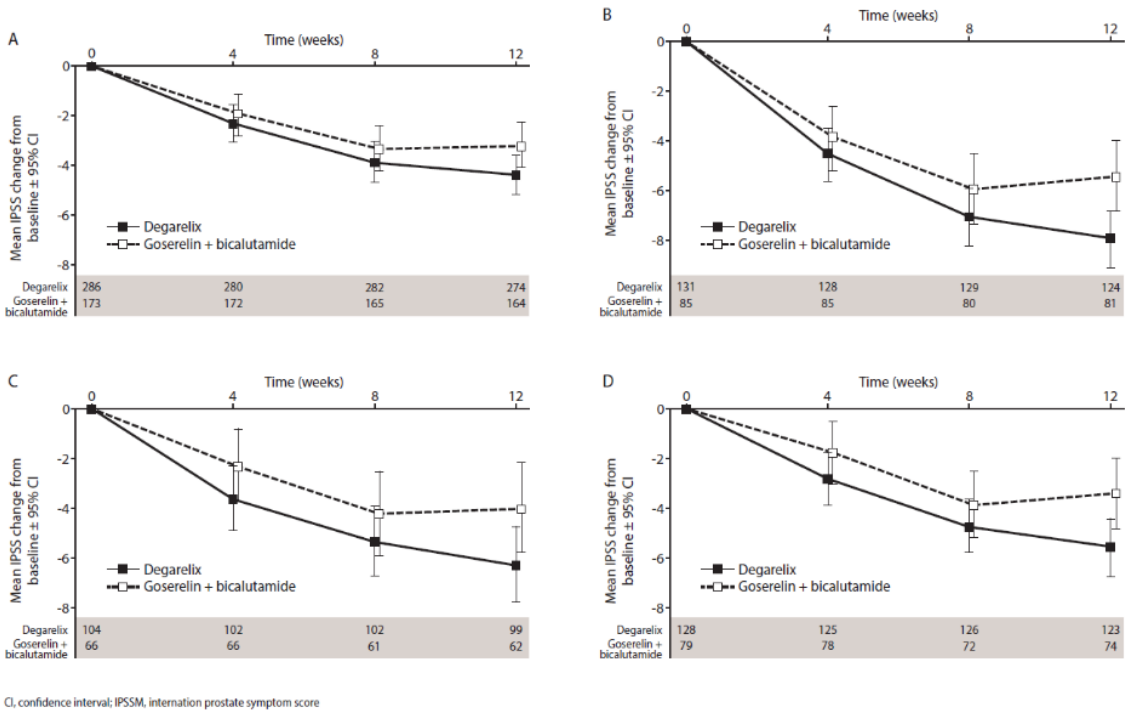
5. FIGURE LEGEND

Figure 1 Longitudinal adjusted mean change in IPSS from baseline to week 12 in (A) the overall patient population, (B) patients with IPSS ≥13 at baseline, (C) patients with dominance of voiding at baseline and (D) patients with advanced cancer stage at baseline.



CI, confidence interval; IPSS, international prostate symptom score.

TABLE 1. Summary of individual Phase 3b trials

	CS28	CS30	CS31
NCT identifier†	00831233	00833248	00884273
n (degarelix/goserelin + bicalutamide	40 (27/13)	244 (180/64)	179 (82/97)
Primary endpoint	Change in IPSS at week 12 vs. baseline	Mean percentage reduction in TPV from baseline at week 12	
PCa stage	Mostly advanced	No metastatic patients	All stages
Baseline PSA (ng/ml)	>2	>2	>2
TPV (ml)	>30	>30	>30
Baseline IPSS	≥12	Any	Any

†www.clinicaltrials.gov.

IPSS, international prostate symptom score; PCa, prostate cancer; PSA, prostate-specific antigen; TPV, total prostate volume.

TABLE 2. Baseline characteristics

Baseline characteristics	**Degarelix (*n* = 289)**	**Goserelin/bicalutamide (*n* = 174)**
Age, years, mean (SD)	70.9 (7.0)	72.1 (6.9)
BMI, mean (SD)	27.4 (4.0)	26.6 (3.7)
Testosterone (ng/ml), mean (SD)	4.2 (1.7)	4.4 (1.6)
PSA (ng/ml), mean (SD)	114 (535)	96 (338)
PCa stage, *n* (%)		
Localised	139 (48)	73 (42)
Locally advanced	97 (34)	44 (25)
Metastatic	32 (11)	35 (20)
Not classifiable	21 (7)	22 (13)
Gleason score, *n* (%)		
≤6	60 (21)	28 (16)
7–10	229 (79)	146 (84)
Total IPSS, mean (SD)	11.9 (7.5)	12.2 (7.7)
Total IPSS score, *n* (%)		
<13	155 (54)	88 (51)
≥13	131 (46)	85 (49)
≥20	44 (15)	26 (15)
TPV, mean (SD)	52.3 (22.9)	50.9 (16.8)
TPV ≤40cc, *n* (%)	110 (38)	54 (31)
TPV >40cc, *n* (%)	179 (62)	120 (69)
IPSS category, *n* (%)		
Dominance of storage	166 (58)	100 (58)
Dominance of voiding	104 (36)	66 (38)
Equal symptoms	16 (6)	7 (4)

BMI, body mass index; IPSS, international prostate symptom score; PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation; TPV, total prostate volume.

TABLE 3. Adjusted mean treatment differences in IPSS during the 12-week treatment period between degarelix and goserelin patients

	Mean treatment difference [95% CI] p-value[†]			
	Week 4	**Week 8**	**Week 12**	**Average**
Overall	-0.351 [-1.32; 0.62] 0.477	-0.55 [-1.59; 0.50] 0.304	-1.24 [-2.33; -0.14] 0.027	-0.71 [-1.61; 0.19] 0.121
LUTS subgroups				
Moderate-to-severe	-0.673 [-2.25; 0.90] 0.401	-1.12 [-2.84; 0.60] 0.199	-2.56 [-4.34; -0.79] 0.005	-1.45 [-2.90; 0.00] 0.050
Dominance of voiding	-1.31 [-3.00; 0.37] 0.126	-1.10 [-3.10; 0.91] 0.281	-2.30 [-4.51; -0.09] 0.042	-1.57 [-3.27; 0.13] 0.070
TPV ≥40 ml	0.05 [-1.15; 1.26] 0.930	-0.61 [-1.90; 0.67] 0.349	-1.02 [-2.37; 0.33] 0.138	-0.53 [-1.65; 0.60] 0.358
PCa subgroups				
Localised[‡]	0.28 [-1.25; 1.81] 0.719	-0.40 [-1.99; 1.20] 0.622	-0.47 [-2.11; 1.16] 0.568	-0.20 [-1.61; 1.21] 0.782
Advanced PCa[§]	-1.04 [-2.44; 0.36] 0.145	-0.87 [-2.40; 0.67] 0.267	-2.17 [-3.83; -0.51] 0.011	-1.36 [-2.67; -0.04] 0.043

[†]IPSS mean estimates adjusted for: treatment, month, study and PCa stage (non-classifiable, localised, locally advanced, metastatic), baseline IPSS, age, BMI, log PSA, testosterone, and TPV. To describe the changes throughout the treatment period, the model also included a treatment-by-month interaction. p-values are based on the t-test.

[‡]Mean estimates not adjusted for PCa stage (otherwise adjustments as above).

[§]Mean estimates adjusted for PCa stages locally advanced or metastatic (otherwise adjustments as above).

BMI, body mass index; CI, confidence interval; IPSS, international prostate symptom score; LUTS, lower urinary tract symptoms; PCa, prostate cancer; PSA, prostate-specific antigen; TPV, total prostate volume.

TABLE 4. Adjusted odds ratios for clinically relevant LUTS relief (≥3-point IPSS decline) during the 12-week treatment period between degarelix and goserelin patients

	Odds ratio [95% CI] p-value†			
	Week 4	**Week 8**	**Week 12**	**Average**
Overall	2.02 [1.14; 3.60] 0.016	1.38 [0.85; 2.24] 0.187	1.52 [0.92; 2.51] 0.104	1.62 [1.06; 2.47] 0.025
LUTS subgroups				
Moderate-to-severe	3.01 [1.55; 5.83] 0.001	1.89 [1.00; 3.55] 0.049	2.31 [1.19; 4.47] 0.013	2.36 [1.42; 3.92] 0.001
Dominance of voiding	3.38 [1.51; 7.59] 0.003	1.48 [0.67; 3.27] 0.334	2.26 [1.00; 5.09] 0.050	2.24 [1.16; 4.35] 0.017
TPV ≥40 ml	2.06 [1.08; 3.91] 0.027	1.68 [0.93; 3.05] 0.086	1.77 [0.94; 3.33] 0.076	1.83 [1.10; 3.05] 0.020
PCa subgroups				
Localised‡	0.99 [0.40; 2.42] 0.980	1.33 [0.62; 2.85] 0.461	0.93 [0.45; 1.95] 0.856	1.07 [0.54; 2.11] 0.842
Advanced PCa§	4.08 [1.75; 9.51] 0.001	1.45 [0.72; 2.96] 0.301	2.36 [1.10; 5.04] 0.027	2.41 [1.32; 4.41] 0.004

†Odds ratios adjusted for: treatment, month, study and PCa stage (non-classifiable, localised, locally advanced, metastatic), baseline IPSS, age, BMI, log PSA, testosterone, and TPV. To describe the changes throughout the treatment period, the model also included a treatment-by-month interaction. p-values are based on the Wald test.

‡Odds ratios not adjusted for PCa stage (otherwise adjustments as above).

§Odds ratios adjusted for PCa stages locally advanced or metastatic (otherwise adjustments as above).

BMI, body mass index; CI, confidence interval; IPSS, international prostate symptom score; LUTS, lower urinary tract symptoms; PCa, prostate cancer; PSA, prostate-specific antigen; TPV, total prostate volume.

TABLE 5. Treatment-emergent renal or urinary tract adverse events† with an incidence of at least 2%

	Degarelix, *n* (%)	**Goserelin/bicalutamide, *n* (%)**
Safety analysis set	292 (100)	175 (100)
Any renal or urinary tract events	38 (13)	17 (10)
Infections and infestations	11 (4)	7 (4)
Urinary tract infection	6 (2)	4 (2)
Renal and urinary disorders	29 (10)	11 (6)
Excessive frequency (pollakiuria)	11 (4)	3 (2)
Nocturia	5 (2)	4 (2)
Dysuria	7 (2)	–

†Classified by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term.