Title:

Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate- to high-risk prostate cancer: A randomised non-inferiority trial of Degarelix versus Goserelin plus Bicalutamide

Authors:

M. Mason, X. Maldonado Pijoan, C. Steidle, S. Guerif, T. Wiegel, E. van der Meulen, P.B.F. Bergqvist, V. Khoo

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Original Article

Neoadjuvant Androgen Deprivation Therapy for Prostate Volume Reduction, Lower Urinary Tract Symptom Relief and Quality of Life Improvement in Men with Intermediate- to High-risk Prostate Cancer: A Randomised Non-inferiority Trial of Degarelix versus Goserelin plus Bicalutamide

M. Mason [*], X. Maldonado Pijoan [†], C. Steidle [‡], S. Guerif [§], T. Wiegel [¶], E. van der Meulen [||], P.B.F. Bergqvist [||], V. Khoo [**]

[*] *Cardiff University, Section of Oncology & Palliative Medicine, Velindre Hospital, Cardiff, UK*
[†] *Hospital Universitari Vall d'Hebron, Servicio de Oncología Radioterápica, Barcelona, Spain*
[‡] *Northeast Indiana Research, Fort Wayne, Indiana, USA*
[§] *CHU, Brachytherapy Unit/Oncology Radiotherapy/PRC, Poitiers, France*
[¶] *Department of Radiation Oncology, University Hospital, Ulm, Germany*
[||] *Ferring Pharmaceuticals A/S, Copenhagen, Denmark*
[**] *The Royal Marsden NHS Foundation Trust & Institute of Cancer Research, London, UK*

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Abstract

Aims: The treatment of intermediate- to high-risk prostate cancer with radical radiotherapy is usually in combination with neoadjuvant androgen deprivation therapy. The aim of the present trial was to investigate whether degarelix achieves comparable efficacy with that of goserelin plus bicalutamide as neoadjuvant therapy before radiotherapy.

Materials and methods: The study was a randomised, parallel-arm, active-controlled, open-label trial in 244 men with a UICC prostate cancer TNM category T2b–T4, N0, M0, Gleason score ≥7, or prostate-specific antigen ≥10 ng/ml and a total prostate volume >30 ml, who were scheduled to undergo radical radiotherapy and in whom neoadjuvant androgen deprivation therapy was indicated. Eligible patients received treatment with either monthly degarelix (240/80 mg) or goserelin (3.6 mg) for 12 weeks, the latter patients also receiving bicalutamide (50 mg) for 17 days initially. The primary efficacy measure was the mean percentage reduction in total prostate volume from baseline at week 12 measured by transrectal ultrasound. The severity and relief of lower urinary tract symptoms were assessed by the International Prostate Symptom Score questionnaire. Quality of life was assessed by the eighth question of the International Prostate Symptom Score. About 50% of the patients had moderate to severe lower urinary tract symptoms at baseline.

Results: The total prostate volume decreased significantly from baseline to week 12 in both treatment groups, reaching −36.0 ± 14.5% in degarelix-treated patients and −35.3 ± 16.7% in goserelin-treated patients (adjusted difference: −0.3%; 95% confidence interval: −4.74; 4.14%). At the end of the therapy, more degarelix- than goserelin-treated patients reported International Prostate Symptom Score decreases of ≥3 points (37% versus 27%, $P = 0.21$). In addition, in patients with a baseline International Prostate Symptom Score of ≥13, the magnitude of the decrease was larger in degarelix- ($n = 53$) versus goserelin-treated patients ($n = 17$) (6.04 versus 3.41, $P = 0.06$).

Conclusions: The efficacy of degarelix in terms of prostate shrinkage is non-inferior to that of goserelin plus bicalutamide. The added benefits of degarelix in terms of more pronounced lower urinary tract symptom relief in symptomatic patients could be the reflection of differences in the direct effects on extra-pituitary receptors in the lower urinary tract [Clinicaltrials.gov ID: NCT00833248].

Key words: Prostate cancer; prostate volume reduction; short-term androgen deprivation; urinary symptom management

Introduction

The treatment of intermediate- to high-risk prostate cancer with radiotherapy is usually in combination with

Author for correspondence: M. Mason, Cardiff University School of Medicine, Institute of Cancer & Genetics, Velindre Hospital, Cardiff CF14 2TL, UK. Tel: +44-29-2031-6964x6964 (office); Fax: +44-29-2052-2694.
E-mail address: MasonMD@cf.ac.uk (M. Mason).

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neoadjuvant androgen deprivation therapy (ADT). Apart from the radiobiologically synergistic action between ADT and radiotherapy [1], one of the reasons for neoadjuvant ADT, in patients in all risk groups, is to decrease prostate volume before radiotherapy, thus decreasing the dose in critical organs, which results in a safer and more effective procedure [2]. Neoadjuvant ADT before radiotherapy can lead, on average, to a 25–30% reduction in prostate size [3,4].

The clinical benefits of neoadjuvant ADT are highlighted by several recent reports. In the Radiation Therapy Oncology Group 86-10 study, radiotherapy with or without combined androgen blockade (goserelin and flutamide) in men with bulky localised and locally advanced prostate cancer resulted in a significantly reduced 5 year incidence of local progression versus radiotherapy alone [5]. Similarly, the 5 year progression-free survival with normal prostate-specific antigen (PSA) levels was significantly greater with neoadjuvant ADT than without. Recent results from the same study showed a trend to improved 10 year overall survival in the neoadjuvant ADT arm, although the differences were not statistically significant [6]. In addition, disease-specific mortality, distant metastasis, disease-free survival and biochemical failure were all significantly superior in the neoadjuvant ADT arm. In the Trans-Tasman Radiation Oncology Group 96.01 trial, 10 year data showed that 3 and 6 months of neoadjuvant ADT (goserelin and flutamide) in men with localised and locally advanced prostate cancer resulted in significantly reduced PSA progression, local progression and improved event-free survival compared with radiotherapy alone [7].

Gonadotrophin-releasing hormone (GnRH) agonists are widely used but cause an initial stimulatory effect on GnRH receptors, which results in a rapid release of gonadotrophins and testosterone. This testosterone surge ('flare') may not only delay the onset of androgen deprivation, but also carry a risk of complications, such as spinal cord compression, bladder outlet obstruction and exacerbation of pain in high-risk metastatic patients [8]. To avoid such complications, anti-androgens are commonly co-administered with the GnRH agonist [9]. In contrast to agonists, the blockade of GnRH receptors by antagonists such as degarelix results in a rapid, marked and sustained suppression of testicular testosterone production without the need for concomitant medication [10]. There are currently no published comparative data of the use of a GnRH antagonist as compared with the combined use of a GnRH agonist and anti-androgens in the neoadjuvant setting [11].

The primary objective of the present trial was to compare the effect of 3 month neoadjuvant therapy with degarelix versus goserelin plus bicalutamide, on total prostate volume (TPV) reduction in men with intermediate- to high-risk prostate cancer who were scheduled to undergo subsequent radiotherapy. Secondary objectives included the effect on lower urinary tract symptom (LUTS) relief and changes of quality of life related to urinary symptoms.

Materials and Methods

Trial Design and Patients

The trial was a randomised, parallel-arm, active-controlled, open-label trial. Main inclusion criteria were: UICC prostate cancer TNM category T2b-T4, N0, M0, Gleason score $\geq$7, or PSA $\geq$10 ng/ml; TPV >30 ml; scheduled to undergo radical radiotherapy treatment and in whom neoadjuvant ADT was indicated. Major exclusion criteria were previous treatment for prostate cancer or transurethral resection of the prostate; use of a urethral catheter; treatment with a 5-alpha reductase inhibitor (finasteride or dutasteride) in the past 12 and 16 weeks, respectively; or treatment with an alpha-adrenoceptor blocker in the past 4 weeks. The trial was approved by the appropriate ethical committees related to the institutions in which it was carried out and all patients gave written consent to participate.

Treatments

Eligible patients were randomised in a 3:1 ratio to receive treatment with degarelix or goserelin for 12 weeks. For patients in the degarelix group, a starting dose of 240 mg (40 mg/ml) was given on day 0 [10]. The second and third doses (maintenance doses) of 80 mg (20 mg/ml) were given on days 28 and 56, respectively. For patients in the control arm, once-daily treatment with bicalutamide 50 mg as anti-androgen flare protection was initiated on day 0 and this treatment continued for 17 days. On day 3, the first goserelin implant (3.6 mg) was administered and the second and third doses were given on days 31 and 59, respectively.

Baseline Parameters

Baseline parameters included demographic data, medical history, medications, vital signs, electrocardiography, the Eastern Cooperative Oncology Group performance score and history of prostate cancer. Blood and urine were also collected to establish baseline values for assessing the changes in efficacy and safety parameters.

Efficacy Assessments

TPV was assessed by transrectal ultrasound using adequate, well-maintained locally available equipment. A user manual for standardised transrectal ultrasound measurements was provided to all sites. Follow-up measurements for each study participant were carried out using the same equipment. The severity of LUTS and changes during therapy were assessed by the International Prostate Symptom Score (IPSS) questionnaire [12]. The IPSS was recorded before dosing at baseline and at week 4, 8, and 12. Mild, moderate, and severe LUTS were defined as an IPSS of 1–7, 8–19 and 20–35, respectively [13]. LUTS relief was also stratified for patients with a baseline IPSS $\geq$13 [14]. A clinically

meaningful response was defined as an IPSS change of at least three points [15]. Overall quality of life related to urinary symptoms was assessed by a separate eighth IPSS question ('If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?'). The answers to this question ranged from 'delighted' (a score of 0) to 'terrible' (a score of 6).

Testosterone and Prostate-specific Antigen

Testosterone and PSA were measured at each monthly visit. Testosterone was measured at a central laboratory (Esoterix CTS, Belgium) and at Ferring Pharmaceuticals A/S (Denmark). PSA was measured at Esoterix CTS, Belgium.

Safety Analysis

Safety assessments included local tolerability, adverse events, adverse drug reactions, physical examinations, vital signs and body weight measurements.

Statistical Analysis

Patients who received at least one dose of the investigational drug and had at least one efficacy assessment were included in the full analysis set (FAS). The per-protocol population was obtained by excluding patients who fulfilled any pre-set criteria for exclusion from the per-protocol analysis set. The primary efficacy measure was the mean percentage reduction in TPV from baseline at week 12. Changes were analysed by analysis of covariance (ANCOVA) for both the FAS and per-protocol populations. Non-inferiority was established if the treatment difference in adjusted mean percentage reduction was significantly greater than $\Delta = -10$ points in both the FAS and per-protocol analysis sets (two-sided at $\alpha = 0.05$ level). Changes in IPSS from baseline were analysed by ANCOVA. Changes in quality of life due to urinary symptoms were analysed by polytomous regression. In total, 228 (171 degarelix and 57 goserelin) patients were required in order to show non-inferiority with 90% probability (assuming a standard deviation of the change from baseline of 20 percentage points at week 12). An additional 5% of anticipated protocol violators were added to arrive at the total of 240 patients.

Results

Patient Disposition and Baseline Characteristics

Patient disposition throughout the trial is outlined in the CONSORT diagram in Figure 1.

The demography of the patients was characteristic of a male population with prostate cancer and there were no clinically significant differences in the baseline variables between treatment groups (Table 1). Overall, the median age was 71 years, the median weight was 80.3 kg, and the median body mass index was 27.0 kg/m^2. Furthermore, 92% of the patients were white and 7% were black.

Mean Percentage Change in Total Prostate Volume

TPV decreased significantly from baseline to week 12 in both treatment groups with mean (± standard deviation) percentage changes of −36.0 ± 14.5% and −35.3 ± 16.7% for degarelix and goserelin, respectively, for the FAS and −36.2 ± 14.5% and −35.4 ± 16.9% for degarelix and

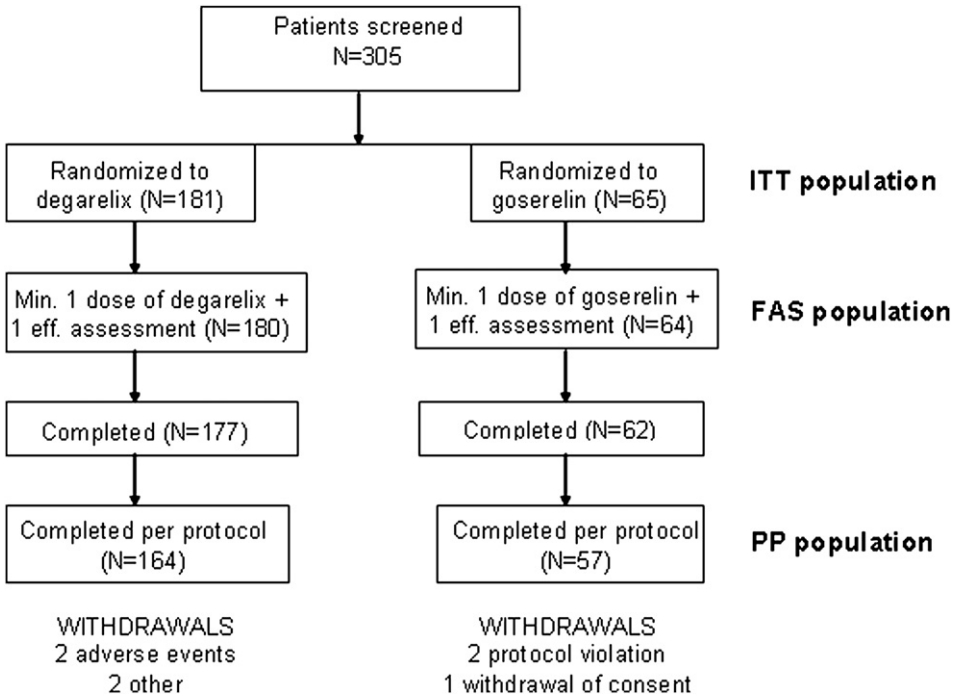

Fig 1. CONSORT diagram of the trial.

Table 1
Baseline characteristics of the trial population [mean ± standard deviation or median with range (minimum–maximum)]

Baseline characteristics	Degarelix	Goserelin/ bicalutamide
Full analysis set	180	64
Age (years)	70.6 (6.37)	70.8 (5.96)
Weight (kg)	83.6 (14.2)	80.9 (12.4)
Body mass index (kg/m^2)	27.8 (3.99)	26.8 (3.69)
Time since prostate cancer diagnosis (days)	75 (14–1378)	72 (17–1526)
Tumour stage*		
Localised	111 (62%)	41 (64%)
Locally advanced	63 (35%)	20 (31%)
Not classifiable	6 (3%)	3 (5%)
T1/2a	5 (83%)	1 (33%)
T3/4	1 (17%)	1 (33%)
TX		1 (33%)
Gleason score		
2–6	41 (23%)	12 (19%)
7	97 (54%)	42 (66%)
8–10	42 (23%)	10 (16%)
ECOG score		
Fully active	154 (86%)	58 (91%)
Restricted, but ambulatory	21 (12%)	6 (9%)
Ambulatory, unable to work	5 (3%)	0
Capable of only limited self-care	0	0
Total prostate volume (ml)	50.9 (20.3)	52.5 (18.8)
IPSS	9.5 (6.71)	8.5 (6.30)
IPSS quality of life	2.27 (1.63)	1.94 (1.56)
Mean PSA (ng/ml)	17.4 (30.1)	13.4 (12.9)
Median PSA	10.0 (2.5–339)	9.75 (2.9–80)
Mean testosterone (ng/ml)	4.18 (1.72)	4.45 (1.49)
Median testosterone	3.92 (0.58–11.2)	4.42 (0.19–8.16)

ECOG, Eastern Cooperative Oncology Group; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.
* Localised = T1 or T2 and (NX or N0) and M0; locally advanced = T3 or T4 and (NX or N0) and M0 or (N1 & M0).

goserelin, respectively, for the per-protocol analysis set (Figure 2). The adjusted differences between treatment groups were −0.3% (95% confidence interval −4.74; 4.14%) for the FAS and −0.27% (95% confidence interval −5.05; 4.52%) for the per-protocol analysis set. The upper limits of the two-sided 95% confidence interval for the adjusted mean differences were thus below the non-inferiority margin of 10, and non-inferiority was considered to have been established.

Changes from Baseline in Serum Testosterone and Prostate-specific Antigen

The median levels of serum testosterone showed no differences between degarelix- and goserelin-treated patients during the trial (Figure 3a). The median level of testosterone for degarelix-treated patients at weeks 4, 8 and 12 was 0.05 ng/ml and the corresponding figures for goserelin were 0.17, 0.05 and 0.05 ng/ml, respectively.

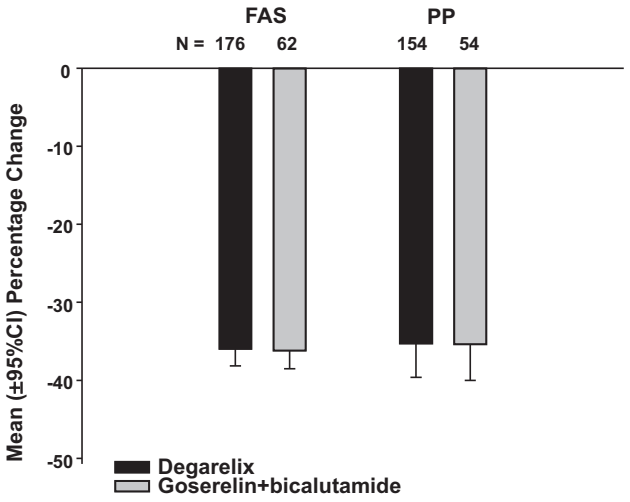

Fig 2. Mean percentage change (±95% confidence interval) in prostate volume measured with transrectal ultrasound at 12 weeks compared with baseline using transrectal ultrasound: full analysis set (FAS) and per-protocol analysis set (PP) (observed case).

Overall, there were seven (of 180) and five patients (of 64) on degarelix and goserelin, respectively, with a serum testosterone level >0.5 ng/ml on at least one occasion. The estimated cumulative probabilities of testosterone ≤0.5 ng/ml between days 28 and 84 were 96% for the degarelix treatment group and 92% for the goserelin treatment group.

The median percentage changes in PSA were also comparable; for degarelix the decreases from baseline at weeks 4, 8 and 12 were −71.6, −84.8 and −89.2%, respectively, whereas for goserelin they were −72.2, −93.1 and −93.0% (Figure 3b).

Changes from Baseline in International Prostate Symptom Score

About 50% of patients had no to mild LUTS, about 40% had moderate and 10% had severe LUTS at baseline. In patients with moderate LUTS at baseline, the mean IPSS (± standard error of the mean) decreased clinically meaningfully (−2.99 ± 0.68, $n = 72$) in degarelix-treated patients by week 12, whereas it remained virtually unchanged in goserelin-treated patients (−0.48 ± 1.29, $n = 23$, $P = 0.06$). In patients with severe LUTS at baseline, the mean IPSS changes from baseline to week 12 were numerically larger in degarelix-treated patients (−6.84 ± 1.31, $n = 19$) compared with goserelin-treated patients (−3.50 ± 3.18, $n = 6$), but differences did not reach statistical significance ($P = 0.21$). Similarly, when focusing on patients with a baseline IPSS ≥13 (a commonly used threshold in clinical trials on LUTS management), degarelix elicited more pronounced LUTS relief compared with goserelin (−6.04 ± 0.79, $n = 53$ versus −3.41 ± 1.23, $n = 17$; $P = 0.06$).

In the total population, 37% of patients in the degarelix group and 27% in the goserelin group experienced clinically meaningful IPSS decreases of at least three points ($P = 0.06$). The mean change (± standard error of the mean) from baseline in IPSS was larger in the degarelix group compared with the goserelin group at weeks 8 (−1.53 ± 0.41, $n = 178$ versus

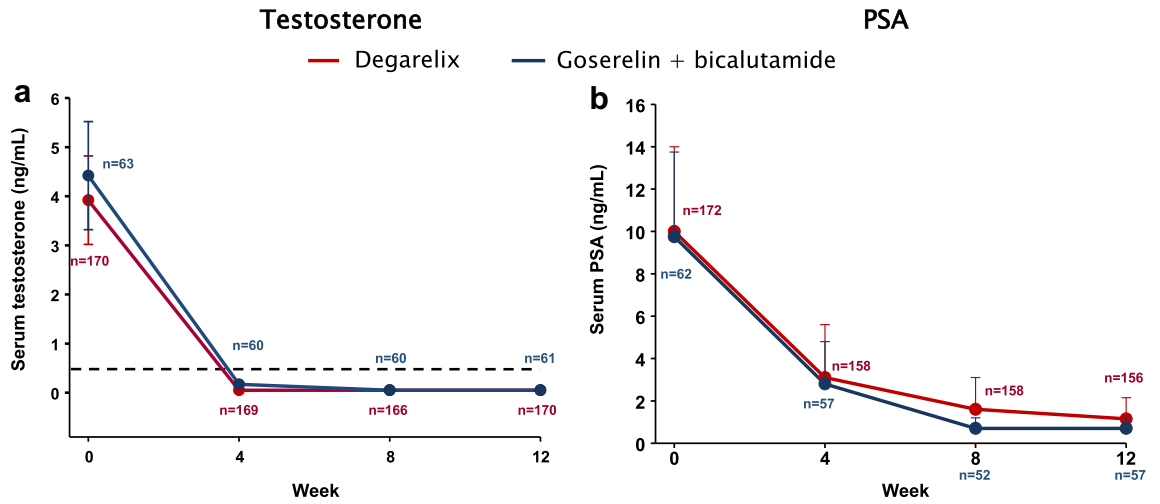

Fig 3. Median (±interquartile range) absolute values (ng/ml) for serum (a) testosterone and (b) prostate-specific antigen (PSA) during the 12 week treatment period.

0.016 ± 0.68, $n = 63$) and 12 (−1.71 ± 0.42, $n = 178$ versus 0.11 ± 0.65, $n = 63$). At week 12, the adjusted (for baseline IPSS) difference between degarelix and goserelin was statistically significant (−1.42 [−2.81; −0.035], $P = 0.044$) (Figure 4).

Change from Baseline in Quality of Life due to Urinary Symptoms

The relative increases in the reporting of 'delighted' or 'pleased' from baseline to week 12 were greater in the degarelix-treated patients compared with goserelin-treated patients (31% versus −3%) and the relative decreases in the reporting of 'unhappy'/'terrible' from baseline to week 12 were also greater in the degarelix-treated patients compared with goserelin-treated patients (−37% versus 14%). However, the numerical differences did not reach statistical significance.

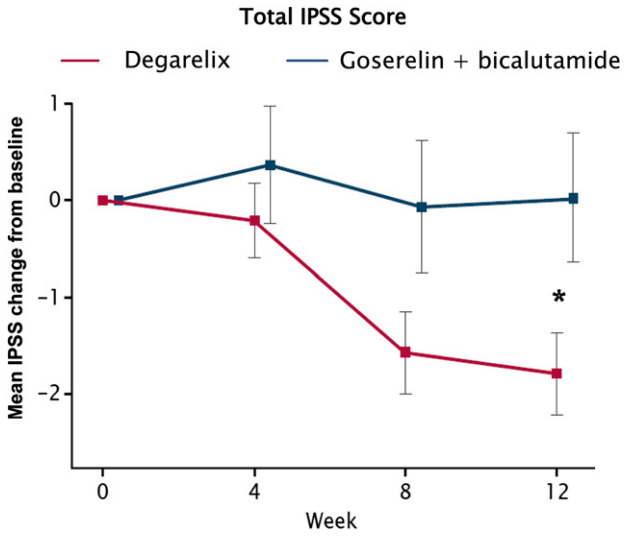

Fig 4. Mean (± standard error of the mean) changes in International Prostate Symptom Score (IPSS) from baseline to degarelix or goserelin plus bicalutamide in prostate cancer patients during the 12 week treatment period. *Statistically significant difference between the groups ($P < 0.05$).

Safety

Treatment-emergent adverse events were reported by 87 and 83% of patients in the degarelix and goserelin groups, respectively. Treatment-emergent adverse events that were considered possibly/probably related to the drug (i.e. adverse drug reactions) were reported by 78 and 73% of patients in the degarelix and goserelin groups, respectively (Table 2). Most of the treatment-emergent adverse drug reactions were hot flushes (60% degarelix, 63% goserelin). Other commonly reported reactions were injection site

Table 2
Incidences of adverse drug reactions occurring in ≥5% of any group by MedDRA system organ class and preferred term

MedDRA system organ class/preferred term	Degarelix	Goserelin/ bicalutamide
Safety analysis set	181 (100%)	64 (100%)
Any adverse drug reaction*	142 (78%)	47 (73%)
Gastrointestinal disorders		
Nausea	2 (1%)	3 (5%)
General disorder and administration site conditions		
Injection site pain	60 (33%)	1 (2%)
Injection site erythema	45 (25%)	0 (0%)
Asthenia	13 (7%)	6 (9%)
Injection site pruritus	13 (7%)	0 (0%)
Injection site swelling	11 (6%)	0 (0%)
Fatigue	10 (6%)	6 (9%)
Injection site induration	9 (5%)	0 (0%)
Psychiatric disorders		
Libido decreased	12 (7%)	4 (6%)
Reproductive system and breast disorders		
Erectile dysfunction	14 (8%)	6 (9%)
Vascular disorders		
Hot flush	108 (60%)	40 (63%)

* An adverse event with a causality assessed as possibly or probably related to treatment.

reactions (predominantly pain 33%, erythema 25%, pruritus 7% and swelling 6%), which were reported by degarelix-treated patients only, erectile dysfunction (8% degarelix, 9% goserelin), asthenia (7 and 9%), fatigue (6 and 9%) and decreased libido (7 and 6%). Serious adverse events considered as probably/possibly related to treatment by the investigator were reported in two patients in the degarelix group and the events included liver enzyme elevations (four reports from one patient) and urinary retention (one report from one patient).

Discussion

The main objective of the present trial was to compare TPV reduction, LUTS relief and related quality of life improvement to 12 week treatment with degarelix or goserelin plus bicalutamide in men with intermediate- to high-risk prostate cancer who were scheduled to undergo subsequent radical radiotherapy. The main finding of the study was the demonstration of the non-inferiority of degarelix to goserelin plus bicalutamide in terms of treatment-induced TPV reduction with some added benefits in terms of LUTS relief, suggesting potential differences in the mechanism of action of these drug classes.

The magnitude of TPV reductions from baseline at week 12 was in the same range reported by similar short-term studies on GnRH agonists (21–54%) [16–21] and in one study on degarelix in patients with more advanced prostate cancer [22]. This rapid and pronounced TPV reduction may not only facilitate better delivery of radiotherapy, but could also contribute to symptom relief in patients with LUTS. In support, Mommsen and Petersen [23] showed that 62% of prostate cancer patients with acute urinary retention regained their voiding ability within 3 months after surgical castration. Similarly, in a small cohort study in 77 prostate cancer patients, Klarskov *et al.* [24] documented statistically significant changes from baseline in numerous objective measures of voiding when treated with different forms of hormone therapy for 12 months; the bulk of the benefit emerging during the first months of the therapy. Because GnRH agonists can improve LUTS in benign prostatic hyperplasia patients [25] the effect of ADT may relate to an overall shrinkage of the prostate rather than tumour volume reduction *per se*.

To assess whether the GnRH antagonist and agonist act similarly in the management of LUTS in patients undergoing neoadjuvant hormone therapy, we compared the percentage of responders and the magnitude of effects between different subgroups with clinically meaningful symptoms at baseline. In alignment with a recent report on more severe prostate cancer patients undergoing 3 month treatment with the same agents [22], we found statistically significant differences in IPSS changes elicited by these drugs despite similar testosterone and PSA suppression. Furthermore, when focusing on those with at least moderate LUTS at baseline, the magnitude of IPSS decreases was consistently larger in degarelix- versus goserelin-treated patients. Because patients undergoing radiotherapy often face LUTS as a complication, the advantages of a GnRH antagonist versus an agonist in already symptomatic patients in the current study may be worthy of consideration when initiating neoadjuvant hormone therapy. Although GnRH receptors have been shown in the lower urinary tract [26,27], whether the observed differences in LUTS relief are due to differences in the pharmacodynamic action of GnRH agonists and antagonists on these receptors remains to be fully clarified.

Both medications were safe and well tolerated with no major differences in adverse event reports, except, as previously noted, for injection site reactions, which were reported only by degarelix-treated patients. Other adverse events were typical manifestations of testosterone suppression (hot flushes, erectile dysfunction, asthenia, fatigue and decreased libido) and their incidence rate was in line with what can be expected in the elderly receiving short-term ADT [22].

Patients using alpha blockers or dutasteride were excluded from this trial, and no conclusions can therefore be drawn from the present data with regard to the efficacy of degarelix in more symptomatic patients. No urodynamic assessments were made in the trial and, in the future, such data would be a useful adjunct to the only assessment of quality of life related to urinary symptoms, i.e. the eighth question of the IPSS. For the present study, the effects of treatment on IPSS were secondary end points only, the primary end point being volume reduction.

In summary, the primary goal of neoadjuvant ADT – TPV reduction before radiotherapy – is equally achieved with degarelix compared with goserelin plus bicalutamide. In addition, degarelix had more pronounced effects on LUTS in symptomatic patients, pointing out potential differences in direct peripheral effects on the prostate and/or the urinary bladder. Degarelix provides an alternative treatment for prostate cancer patients who need neoadjuvant ADT before radiotherapy, especially for those having or inclined to LUTS problems.

Conflict of Interest

M. Mason is an advisor/speaker for Bristol-Myers Squibb, Caris Biosciences, Ferring, Janssen, sanofi-aventis and Takeda; E. van der Meulen and P.B.F. Bergqvist are employed by Ferring Pharmaceuticals A/S.

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in the collection, analysis and interpretation of the data and in the decision to submit the paper.

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