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Efficacy and safety of degarelix in Korean patients with prostate cancer requiring androgen deprivation therapy: Open-label multicenter phase III study

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ABSTRACT

Purpose: To assess the noninferiority, efficacy, and safety of degarelix in achieving and maintaining testosterone at castrate levels (≤0.5 ng/mL) in Korean patients (CS42) versus non-Asian patients with prostate cancer (PCa).

Methods: A Phase III, open-label, multicenter, single-arm trial was conducted in Korean patients with PCa. Degarelix was administered at a starting dose of 240 mg followed by monthly (28-day intervals) maintenance doses of 80 mg (240/80 mg dose regimen) for 7 months. The results were compared with non-Asian patients receiving degarelix 240/80 mg in the CS21 study.

Results: The estimated difference in the cumulative probabilities of testosterone ≤0.5 ng/mL from Day 28 to Day 196 between the trials was −2.3% (96.7% in CS42 vs. 99.0% in CS21). The lower limit of the 95% confidence interval was −5.5%, i.e., above the predefined noninferiority limit of −10% and thus non-inferiority was established. Decreases in serum testosterone, prostate-specific antigen, and luteinizing hormone over time were similar in CS42 and CS21. There were no clinically significant differences in incidence of treatment-emergent adverse events (72% in CS42 vs. 70% in CS21) and changes in clinical chemistry and hematology parameters between the two trials. The most common adverse event was injection-site reaction.

Conclusions: Overall, degarelix was effective and well tolerated in Korean patients. Testosterone suppression was noninferior to that in non-Asian patients and safety findings were as would be expected for elderly men with PCa undergoing androgen deprivation therapy.

1. Introduction

Androgen deprivation therapy (ADT) is first-line treatment for advanced/metastatic prostate cancer (PCa) and is also recommended in combination with radiotherapy in the management of intermediate and high-risk localized disease.[1] For many years, luteinizing hormone-releasing hormone (LHRH) agonists have formed the mainstay of ADT. However, gonadotrophin-releasing hormone (GnRH) antagonists offer a more recently developed alternative first-line ADT treatment option. The most extensively studied and widely available antagonist worldwide is degarelix. Unlike LHRH agonists, degarelix provides immediate GnRH receptor inhibition resulting in rapid and profound testosterone suppression.[2]

In the pivotal Phase III registration trial (CS21; NCT00295750), conducted in Europe and North America, degarelix displayed similar efficacy to the LHRH agonist leuprolide in suppressing testosterone over 1 year.[3] However, degarelix reduced testosterone and prostate-specific antigen (PSA) more rapidly with no initial testosterone surge or subsequent microsurges, and no requirement for flare protection with antiandrogens. Studies show that response to drug therapy can vary according to ethnicity.[4,5] It is known that racial differences within the androgen/androgen receptor pathway not only exist but also could be causally related to clinically observed differences in the biology of PCa among the ethnicity,

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including responses to ADT.[6] Therefore, clinical pharmacologic drug evaluation should ideally include a population representative of the target therapeutic population. In addition to studies in predominantly non-Asian populations, the efficacy of degarelix has also been studied in Japanese patients.[7]

The aim of the current trial (CS42; NCT01071915) was to establish the efficacy and tolerability of degarelix in Korean patients with PCa and to establish noninferiority of degarelix in Korean patients compared to non-Asian patients treated with the same dose regimen in the pivotal phase III CS21 trial with regard to achieving and maintaining castrate testosterone levels.

2. Methods

2.1. Study design

CS42 was an open-label, multicenter, single-arm trial in Korean patients with PCa. Patients received subcutaneous injections of degarelix 1-month depot at a starting dose of 240 mg (40 mg/mL) followed by monthly (28-day intervals) maintenance doses of 80 mg (20 mg/mL; 240/80 mg dose regimen) for 7 months. The results were to be bridged to those of the 240/80 mg arm of the CS21 trial in non-Asian patients.[3] Degarelix was supplied as a freeze-dried powder for suspension in water.

The trial was conducted in accordance with the Declaration of Helsinki as well as Good Clinical Practice Guidelines. The Institutional Review Board at all participating institutions approved the protocol. All patients provided written informed consent.

2.2. Patients

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

2.3. Assessment

The primary endpoint was the difference in cumulative probability of testosterone suppression to castrate levels (≤0.5 ng/mL) from Day 28 to Day 196 between Korean patients and non-Asian patients treated with the degarelix 240/80 mg dose regimen in the CS21 trial. If noninferiority was established, the secondary objective of showing that 7-month testosterone suppression response rate was significantly >90% in the full analysis set (FAS) in Korean patients was tested; therefore this prioritized secondary endpoint was the cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 196 in Korean patients. Secondary endpoints also included the proportion of patients with testosterone ≤0.5 ng/mL at Day 3, percentage change in PSA from baseline to Day 28, cumulative probability of testosterone ≤0.5 ng/mL from Day 56 to Day 196, serum levels of testosterone, luteinizing hormone (LH) and PSA over time, and cumulative probability of no PSA failure (2 consecutive increases of 50%, and ≥5 ng/mL, compared to nadir). Safety analysis comprised the frequency and severity of adverse events (AEs) and clinically significant changes in laboratory values, electrocardiogram, physical examination, and vital signs. Blood samples for analysis of testosterone, PSA, and LH were collected at each trial visit. At dosing visits, blood sampling was performed predose and, where possible, at the same time of day, preferably in the morning. A central laboratory (SCL, Seoul, Korea) measured serum hormones (testosterone and LH) and PSA in accordance with Good Laboratory Practice, using validated methods.

2.4. Determination of sample size

For sample size calculation, the 95% confidence interval (CI) of the testosterone suppression response rate for the CS21 240/80 mg non-Asian reference population was 95.8–99.7%. Assuming a response rate in Korean patients of 97% (lower than observed point-estimate of 99% but still well within the CI) and a 15% annual drop-out rate, 150 patients are required to have sufficient power (≥90%) in the FAS.

2.5. Statistical analysis

The primary analysis population was the FAS, defined as patients who received the study drug and in whom ≥1 efficacy variable (primary or secondary) was evaluated after administration. Intention-to-treat (ITT) analysis comprised all patients who were allocated to treatment, the per-protocol (PP) analysis was defined as FAS patients who did not violate specific predefined criteria for major protocol deviations which were in line with the CS21 trial, and the safety analysis set comprised patients who received ≥1 degarelix dose.

The primary efficacy endpoint (noninferiority assessment) measuring the difference in cumulative probability of testosterone ≤0.5 ng/mL between Korean (CS42) and non-Asian (CS21) patients receiving degarelix 240/80 mg, was estimated using the Kaplan–Meier (KM) method using testosterone measurements from Day 28 to Day 196. The standard error of this estimate was based on Greenwood's formula. The corresponding 95% two-sided CI was constructed using the pooled standard errors of these estimates. Noninferiority was established if the lower limit of this CI was >−10%. To determine effectiveness in Korean patients (prioritized secondary endpoint), testosterone suppression was considered statistically significant if the lower limit of the two-sided 95% CI was ≥90%. The two-sided 95% CI was derived in the same manner as the primary endpoint.

The difference in proportion of patients with testosterone ≤0.5 ng/mL at Day 3 was tested using Fisher's Exact test ($\alpha = 0.05$, two-sided). Median (interquartile range) percentage change from baseline to Day 28 in PSA was calculated and groups tested using the two-sample Wilcoxon test ($\alpha = 0.05$, two-sided). Cumulative probability of testosterone ≤0.5 ng/mL from Day 56 to Day 196 was estimated by the KM method. Cumulative probability of no PSA failure was estimated using the KM method; groups were compared using the log-rank test ($\alpha = 0.05$, two-sided).

3. Results

3.1. Patient disposition

The study was conducted between March 2010 and November 2011. Of 187 patients screened, 157 were allocated to treatment (ITT). Of these, 156 (99%) received one or more degarelix dose (safety population) and 155 (99%) had one or more efficacy assessment after dosing (FAS). Six FAS patients were excluded from the PP analysis, which comprised 149 (95%) patients. The proportions of patients completing CS42 (148/157; 94%) and 7 months

treatment with degarelix 240/80 mg in CS21 (188/207; 91%) were similar. In CS42, patients ($n = 9$) withdrew due to AEs ($n = 3$), withdrawal of informed consent ($n = 2$), physician decision ($n = 2$), or other reasons ($n = 2$). In the CS21 patient-cohort, nine patients withdrew due to AEs, two were lost to follow-up, and seven discontinued for other reasons. Baseline age, testosterone, and PSA were similar between CS42 and CS21; CS42 patients had higher baseline LH (Table 1). CS42 had slightly more patients with locally advanced PCa and slightly fewer with localized disease; in both studies, >50% of patients had a Gleason score of 7–10.

Since the results for FAS and PP populations were similar, only FAS data are reported.

3.2. Efficacy

3.2.1. Cumulative probability of testosterone at castrate level

The estimated difference in the cumulative probability of testosterone at castrate levels (≤0.5 ng/mL) from Day 28 to Day 196 between Korean patients in CS42 and non-Asian patients in CS21 was −2.3% for the FAS dataset. The lower limit of the 95% CI was −5.5%, i.e., above the predefined noninferiority limit of −10% and noninferiority was thus established and, accordingly, bridging between CS42 and CS21 was successful.

Fig. 1 shows KM estimates for cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 196 in CS42 and CS21 (FAS). In CS42, one patient had a testosterone escape (>0.5 ng/mL) at Day 28 and two additional escapes occurred on Day 112 and Day 196. KM estimates of the cumulative probability of testosterone ≤0.5 ng/mL were 96.7% (95% CI: 92.2–98.6%) in Korean patients (CS42) versus 99.0% (95% CI: 95.9–99.7%) in non-Asian men in CS21 (log-rank test, $p = 0.138$; FAS dataset). Since the lower bound of the 95% CI was above the 90% threshold, degarelix was shown to be effective in achieving and maintaining castrate testosterone levels in Korean patients.

3.2.2. Effect on testosterone over time

Decreases in testosterone over time were similar in CS42 and CS21 (Fig. 2A). At Day 3, median testosterone was 0.26 ng/mL and 0.24 ng/mL in CS42 and CS21, respectively, and median percentage decreases from baseline were 94.0% and 94.2%, respectively. The proportion of patients with testosterone ≤0.5 ng/mL at Day 3 was

Table 1
Baseline patient characteristics.

Characteristic	CS42 ($n = 155$)	CS21 ($n = 207$)
Age (y)	74 (50–92)	72 (51–89)
Body mass index (kg/m^2)	23.8 (16.6–42.2)	25.8 (17.3–42.2)
Testosterone (ng/mL)	4.03 (1.08–10.7)	4.1 (0.73–10.6)
Prostate-specific antigen, (ng/mL)	19.2 (1.59–100)	19.8 (1.7–3187)
Luteinizing hormone (IU/L)	7.9 (0.09–75.9)	5.85 (1.24–28)
Stage of disease at enrolment		
Localized	43 (28)	68 (33)
Locally advanced	60 (39)	64 (31)
Metastatic	39 (25)	37 (18)
Not classifiable	13 (8)	37 (18)
Gleason score		
2–4	–	20 (10)
5–6	24 (16)	68 (33)
7–10	130 (84)	118 (57)
Prior therapy		
Radical prostatectomy	14 (9)	15 (7)
Radiotherapy	7 (5)	22 (11)
Neoadjuvant therapy	4 (3)	12 (6)
Watchful waiting	137 (88)	177 (86)

Data are presented as *n* (%) or median (range).

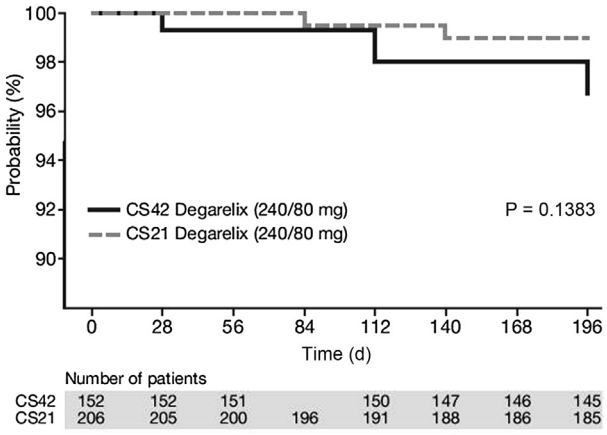

Fig. 1. Kaplan–Meier plot (95% confidence interval) of the cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 196 in patients receiving degarelix 240/80 mg in studies CS42 and CS21 (240/80 mg, non-Asian patients; full analysis set).

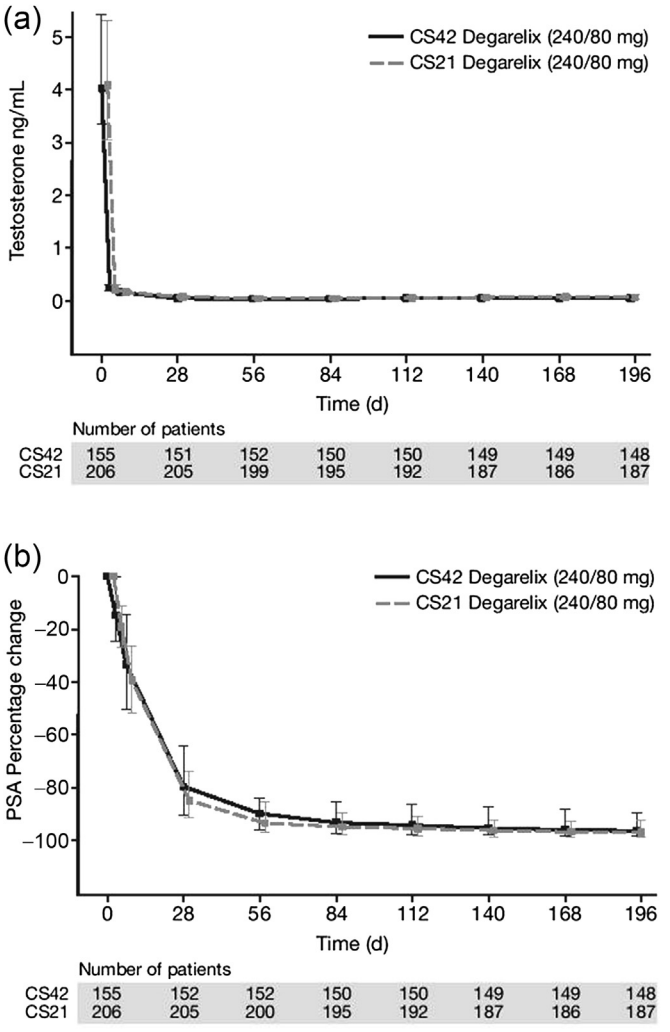

Fig. 2. Secondary endpoints. (**a**) Median (interquartile range) serum testosterone (ng/mL) and (**b**) median (interquartile range) percentage change in serum prostate-specific antigen (PSA; ng/mL), over time in patients receiving degarelix 240/80 mg in CS42 and CS21 (240/80 mg, non-Asian patients; full analysis set).

97.4% in CS42 and 96.1% in CS21 ($p = 0.566$, Fisher's exact test; FAS). At Day 196, very similar decreases in testosterone were observed: median serum testosterone had decreased by 98.4% and 98.1% in CS42 and CS21, respectively (median testosterone at Day 196 was 0.070 ng/mL and 0.086 ng/mL in CS42 and CS21, respectively). In addition, in CS42 and CS21, the KM estimates of the cumulative probabilities of testosterone ≤0.5 ng/mL from Day 56 to Day 196 were 96.7% and 99.0%, respectively (log-rank test, $p = 0.140$; FAS), similar to the results from Day 28 onwards.

3.2.3. Effect on PSA over time

Decreases in serum PSA over time were similar in CS42 and CS21 (Fig. 2B; FAS). The median percentage reductions from baseline to Day 28 in PSA were 79.7% and 85.0% in CS42 and CS21, respectively ($p = 0.030$, Wilcoxon test; FAS). Corresponding decreases at Day 84 were 93.5% and 95.1%, respectively. At Day 196, PSA decreases were 96.2% and 97.0% and the absolute median PSA values were 0.67 ng/mL and 0.60 ng/mL in CS42 and CS21, respectively (FAS).

The cumulative probability of no PSA failure from Day 28 to Day 196 was similar between CS42 and CS21, at 97.3% (95% CI: 93.1–99.0%) and 97.9% (95% CI: 94.5–99.2%), respectively; the estimated difference between groups was not significant (log rank test, $p = 0.723$; FAS). The probability of no PSA failure in CS42 and CS21 was lower in patients with baseline PSA >50 ng/mL (93.8% and 91% vs. 98–100% in lower baseline PSA categories) and in patients with locally advanced (96.7% and 98.4%) and metastatic (94.6% and 91.2%) versus localized (100%) disease (FAS).

3.2.4. Effect on LH over time

Decreases in serum LH over time were similar in CS42 and CS21. The median percentage decrease from baseline to Day 3 in serum LH was 95.7% and 94.8% in CS42 and CS21, respectively. At Day 196, median serum LH had fallen by 98.0% and 98.5%, respectively. The absolute median values at Day 196 were 0.16 ng/mL and 0.09 ng/mL, respectively.

3.3. Safety

Treatment-emergent AEs were reported by 72% of Korean patients in CS42 and 70% of non-Asian patients receiving degarelix 240/80 mg in CS21 (Table 2). The majority of AEs were mild or moderate; severe AEs occurred in 7% of patients in CS42 and this was comparable to the CS21 cohort (12%). Two (1%) patients died during CS42 due to disease progression. There was no difference in overall incidence of deaths between CS42 and CS21 (4 deaths; cardiac arrest in 2 patients, gastric hemorrhage in 1 patient, and bronchopneumonia in 1 patient). No deaths in either trial were considered treatment-related.

Table 2
Incidence of most frequent treatment-emergent adverse events.

Adverse event, *n* (%)	CS42 ($n = 156$)	CS21 ($n = 207$)
Any	113 (72)	144 (70)
Injection-site pain	34 (22)	55 (27)
Hyperhidrosis	14 (9)	–
Injection-site erythema	13 (8)	35 (17)
Constipation	13 (8)	11 (5)
Upper respiratory tract infection	12 (8)	3 (1)
Nocturia	10 (6)	5 (2)
Hot flush[a]	5 (3)	45 (22)
Injection site swelling	4 (3)	10 (5)
ALT increase	3 (2)	16 (8)
Hypertension	1 (<1)	12 (6)

ALT, alanine aminotransferase.
[a] Five (3%) patients also reported flushing in CS42.

The most common AE was injection-site reaction; the majority were injection-site pain and injection-site erythema. Most injection-site reactions were associated with the initial degarelix dose and thereafter were much less frequent. No patient discontinued due to injection-site AEs and none were serious or severe in intensity. Hot flushes occurred in 22% of patients in CS21 versus 3% of patients in CS42 (3% of patients also reported flushing). Hyperhidrosis occurred in 9% of patients in CS42 versus none in CS21.

In CS42, 18 (12%) patients experienced serious AEs (SAEs) of which two (hyperglycemia and atrial fibrillation) were considered possibly related to degarelix. There were no major differences in overall incidence or pattern of SAEs between CS42 and CS21. In CS42, three (2%) patients had an AE that led to discontinuation; all were considered unrelated to degarelix treatment. There were no major differences in the overall incidence of AEs leading to discontinuation between CS42 and CS21 (9 patients, 4%).

No clinically significant differences were observed between the two trials regarding changes in clinical chemistry and hematology parameters from baseline to Day 196.

4. Discussion

Several data suggest that ethnical variations in the serum sex hormone levels and androgen/androgen receptor pathway could contribute to differences in the incidence and biology of PCa.[6,8] Song et al[9] found that a significant proportion of Korean patients with PCa exhibited poor differentiation, regardless of initial serum PSA level or clinical stage at presentation, which resulted in a greater rate of biochemical failure. Salonen et al[10] found that a significant proportion of patients with aggressive and advanced PCa do not respond adequately to ADT. Therefore, we assume that the response to ADT experienced by Korean patients with PCa might differ in other ethnicity.

These data establish the safety and efficacy of degarelix in Korean patients with PCa. Degarelix (240/80 mg regimen) was noninferior with regard to achieving and maintaining testosterone at castrate levels (≤0.5 ng/mL) from Day 28 to Day 196 between Korean patients in CS42 and non-Asian patients in the CS21 trial. Thus, the estimated difference in cumulative probabilities of testosterone at ≤ 0.5 ng/mL from Day 28 to Day 196 between CS42 and CS21 met the predefined noninferiority limit of −10%. The cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 196 in Korean patients was ~97%, similar to that in CS21.

GnRH antagonists bind immediately and competitively to GnRH receptors in the pituitary, providing rapid LH and testosterone suppression.[11] The rapid testosterone suppression with degarelix has been noted in several trials,[3,12,13] and was also observed in the current cohort of Korean patients, with 97.4% achieving castration by Day 3. The rapid testosterone suppression with degarelix contrasts with the delayed suppression observed with LHRH agonists due to an initial testosterone surge, which may cause a transitory exacerbation of clinical symptoms (flare) in advanced disease.[14,15] Also, as GnRH antagonists are not associated with testosterone flare, there is no need for antiandrogen coadministration.[12,13] Moreover, LHRH agonist re-administration can raise testosterone (acute-on-chronic response or microsurge).[16] In CS21, testosterone data on Day 252, Day 255, and Day 259 were analyzed to evaluate testosterone microsurges. Eight patients (4%) receiving leuprolide had microsurges, with testosterone breakthrough (>0.5 ng/mL) occurring in four patients. There were no microsurges in any patient on degarelix.[3] Berges and Bello[17] suggested that an increase in testosterone to >0.5 ng/mL might be clinically relevant, with potential implications for treatment, and Morote et al[18] found a

relationship between poor testosterone control and lower survival free of androgen-independent progression. However, the clinical significance of testosterone microsurges and breakthroughs remains to be fully determined.

Biochemical evidence of clinical improvement in Korean patients was demonstrated with a rapid reduction in PSA (e.g., median 80% reduction from baseline by Day 28). The overall decline in PSA was similar to that in non-Asian patients in CS21 and, furthermore, in terms of PSA control, there was a similar probability of no PSA failure in CS42 and CS21. These similarities in PSA response were apparent despite a slightly higher percentage of high-risk patients and/or patients with advanced PCa in CS42.

The tolerability of degarelix in Korean patients with PCa was confirmed, with comparable safety to that in non-Asian patients receiving degarelix 240/80 mg in CS21. As expected, AEs associated with testosterone suppression, e.g., hot flushes, were observed, although these were tolerable. In CS42, while injection-site reactions were frequent, these were mild or moderate and of little clinical significance. In addition, the incidence of injection-site reactions in CS42 was lower than in CS21. In CS21, although degarelix had a higher rate of injection-site reactions than leuprolide, this difference might reflect different administration routes (subcutaneous degarelix vs. intramuscular leuprolide) and injection volume.[3] The types and incidence of AEs in CS42 were not substantially different from previous clinical studies of ADT. In addition, although the incidence of AEs was slightly higher in CS42 than in CS21, there was no marked difference in the type and occurrence of SAEs and AEs leading to discontinuation.

This present study may have limitations. The open study design is an obvious limitation, especially in the interpretation of reported AEs. However, in this single-arm study, degarelix was administered subcutaneously at one dose and thus blinding was clearly not possible. Another limitation is that the CS42 and CS21 trials were performed independently. Even though two studies were performed as the same design, it might be scientifically unreasonable to compare independently performed studies.

In conclusion, the CS42 trial successfully confirmed the previously demonstrated efficacy of the 1-month degarelix depot by meeting the predefined criterion for noninferiority in testosterone suppression rates between Korean and non-Asian patients. There were rapid decreases in testosterone, PSA, and LH and the serum profiles over time were comparable between CS42 and CS21. Degarelix was well tolerated in Korean patients and in line with what can be expected for elderly men with PCa undergoing ADT. The results of an extension trial of CS42 (CS42A) will provide longer-term safety and tolerability data for degarelix administered up to 1 year in Korean patients with PCa.

Conflicts of interest

All authors have none to declare.

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